A STUDY ON COAGULATION PROFILE OF PATIENTS THROMBOLYSED WITH STREPTOKINASE IN ACUTE ST-ELEVATION MYOCARDIAL INFARCTION

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THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI

MAY 2018

BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled **"A STUDY ON COAGULATION PROFILE OF PATIENTS THROMBOLYSED WITH STREPTOKINASE IN ACUTE ST-ELEVATION MYOCARDIAL INFARCTION"** is a bonafide original work of **Dr. Rojer David Binny V** in partial fulfilment of the requirements of M.D General Medicine [Branch-1] examination of The Tamilnadu Dr.M.G.R Medical University to be held in May 2018.

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DECLARATION

I solemnly declare that the dissertation titled **"A STUDY ON COAGULATION PROFILE OF PATIENTS THROMBOLYSED WITH STREPTOKINASE IN ACUTE ST- ELEVATION MYOCARDIAL INFARCTION"** is done by me at K.A.P.VISWANATHAM GOVT MEDICAL COLLEGE, TIRUCHIRAPALLI-1 under the guidance and supervision of Prof.Dr.N.K.Senthilnathan, M.D. This dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfilment of the requirements for the award of M.D Degree [Branch-1] in General Medicine.

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PLAGIARISM CERTIFICATE

This to certify that this dissertation work titled **"A STUDY ON COAGULATION PROFILE OF PATIENTS THROMBOLYSED WITH STREPTOKINASE IN ACUTE ST- ELEVATION MYOCARDIAL INFARCTION"** of the candidate **Dr. ROJER DAVID BINNY V** with registration number **201511554** for the award of **M D DEGREE** in the branch of **GENERAL MEDICINE**. I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **6%** percentage of plagiarism in the dissertation.

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INTRODUCTION

INTRODUCTION

Myocardial infarction is a leading cause of death in the 21st century. It has assumed epidemic proportions in India. The Global Burden of Diseases (GBD) study reported the estimated mortality from CAD(coronary artery disease) in India at 1.6 million in the year 2000[1]. It has been predicted that by 2020 there would be 11% increase in CV deaths in India.

According to data from Registrar General of India Coronary heart disease (CHD) mortality is greater in south India while stroke is more common in the eastern Indian states. CHD prevalence is higher in urban Indian populations while stroke mortality is similar in urban and rural regions.

WHO(World Health Organization) has predicted that from years 2000 to 2020 disability-adjusted life years lost (DALYs) from CHD in India shall double in both men and women from 7.7 and 5.5 million.

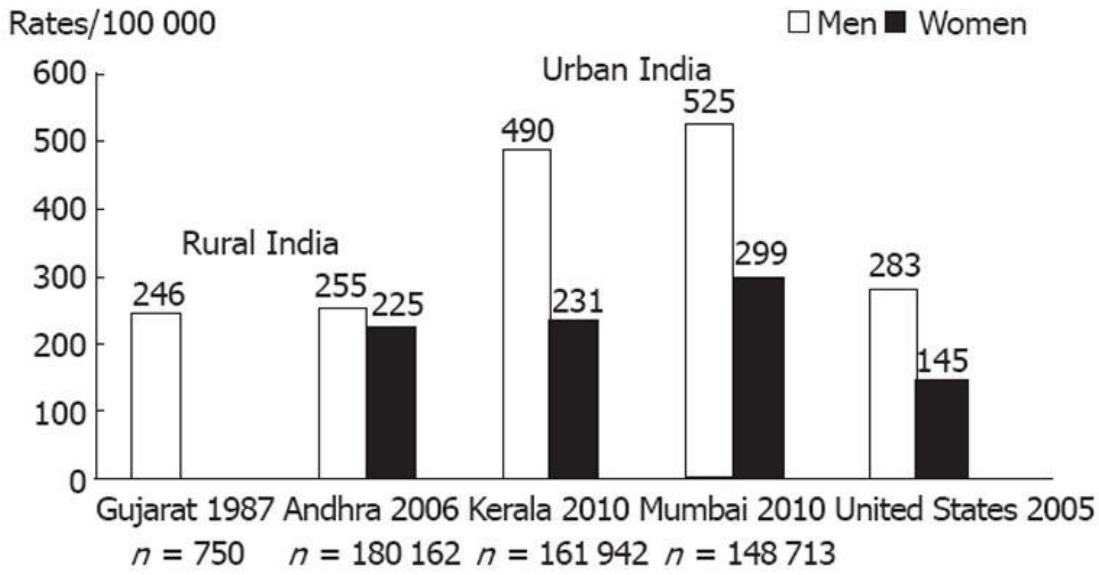
The mortality is highest in south Indian states, eastern and north-eastern states and Punjab in both men and women, while mortality is the lowest in the central Indian states of Rajasthan, Uttar Pradesh and Bihar.

Several risk factors have been associated with CAD .A risk factor is a feature of an individual or population that is present early in life and is associated with an increased risk of developing future disease. Apart from multiple conventional risk factors other factors such as abnormalities of inflammation, hemostasis, and/or thrombosis appear to contribute decisively.

Smoking is a major risk factor for CAD. There are significant state and regional level variations. Smoking was highest in eastern Indian states and lowest in Punjab.The major conventional risk factors include hypertension, diabetes, smoking, hyperlipidemia and obesity. The non conventional risk factors include hsCRP, lipoprotein (a),homocysteine, fibrinogen, D-dimer, tissue plasminogen activator (t-PA) and plasminogen activator inhibitor (PAI- 1).

Hypertension, diabetes and metabolic syndrome were significantly more common risk factors in females whereas males were more likely to be smokers. The prevalence of smoking and tobacco chewing was significantly higher in patients presenting with premature CAD than in elderly patients with CAD.

STEMI was more common than UA(Unstable Angina)/NSTEMI(Non ST Elevation Myocardial Infarction) in smokers than non smokers[2]. Both the incidence and prevalence of CAD are increased in patients who are affected with periodontal disease. Association of premature CAD is seen with dyslipidemia, family history of CAD, smoking and tobacco chewing.



The higher prevalence of cardiovascular risk factors in urban areas in India is in contrast to high income countries where the CVD risk factors are equal in urban and rural areas. There is recent evidence that, in more developed states of India, the rural-urban differences in cardio metabolic risk factors have largely disappeared and the risk factors are equal or slightly greater in rural subjects. In the last 30 years, the prevalence of hypertension and hypercholesterolemia has doubled in India while that of diabetes has trebled.

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES OF STUDY

1. TO FIND THE CHANGES IN THE COAGULATION SYSTEM AFTER THROMBOLYSIS WITH STREPTOKINASE IN ST ELEVATION MYOCARDIAL INFARCTION.

2. TO POSTULATE ABOUT THE TIMING OF STARTING HEPARINISATION AFTER THROMBOLYSIS WITH STREPTOKINASE IN ST ELEVATION MYOCARDIAL INFARCTION.

MATERIALS AND METHODS

Setting:

The study was conducted in medicine department of KAPV govt medical college Trichy.

The total duration of study was 1 year.

Design:

Is a Cross sectional observational study of patients admitted with Acute ST Elevation Myocardial Infarction(STEMI) who were candidates for thrombolysis.

Coagulation assay protocol

Whole blood is collected at baseline and at intervals of 3, 6, & 9hrs following initiation of thrombolysis.

Obtaining the sample

Whole blood is collected into citrated anticoagulant tube containing a fixed amount of citrate as anticoagulant in ratio of one part citrate solution to nine parts of whole blood. Sample is sent to laboratory immediately.

Patient is heparinized at 6 hours irrespective of the results of PT (prothrombin time)/APTT(activated partial thromboplastin time) with UFH(unfractionated heparin) with a loading dose of 5000IU followed by 5000 units q6th hourly for 5 days.

Method of collection of data

A written informed consent was taken for participation after explaining the purpose and design of the study to each subject. The patient prior to consent was informed that refusal to participate in the study would not lead to any detrimental

consequences or affect the treatment there of. A detailed medical history, physical examination and ECG was recorded at the time of arrival of the patient and 90 minutes after thrombolysis.

Inclusion criteria

ALL PATIENTS PRESENTING WITH ACUTE ST SEGMENT ELEVATION MYOCARDIAL INFARCTION PRESENTING WITHIN THE WINDOW PERIOD.

Exclusion criteria

1. THOSE PATIENTS WITH CONTRAINDICATIONS FOR THROMBOLYSIS.
2. THOSE ON ANTICOAGULANTS.
3. THOSE THROMBOLYSED EARLIER.

Statistical analysis

The collected data was summarized in terms of tables, diagrams and charts. Statistical analysis was done using Epi-Info software, version 7.1.2.0. Continuous variables were presented as mean values with Standard Deviation. Categorical variables were compared using Chi square test. A probability value of < 0.05 was considered statistically significant.

TOOLS USED

1. Clinical proforma
2. ECG
3. Measurement of PT/APTT .

REVIEW OF LITERATURE

EPIDEMIOLOGY

The mean age of presentation of CAD in India is 58.32 +/- 11.24 years which is higher than South Asian cohort and males (85.2%) outnumber females (14.8%) in the INTERHEART study[3]. The mean age of presentation was higher in females(64) vs males (57). Hypertension, diabetes and metabolic syndrome were more common risk factors in females whereas males were more likely to be smokers.

Risk factors such as smoking, abnormal lipids, hypertension, diabetes, high waist-hip ratio, sedentary lifestyle, psychosocial stress, and a lack of consumption of fruit and vegetables explained more than 90% of acute CHD events in South Asians.

Smoking is increasing in young population in the 20-35 age group according to national family health survey[4].Smoking rates were higher in eastern states and lowest in Punjab. Prevalence of overweight and obesity was the highest in southern and northern Indian states and the lowest in central Indian states.

A review of epidemiological hypertension studies reported that the prevalence of hypertension was significantly higher in urban populations in India compared with rural populations. Cardiovascular mortality data from India has reported large regional variations with annual mortality rates greater than 250/100 000 in southern and eastern regions of the country and less than 100/100 000 in central India.

In developed states of India such as Kerala, the rural-urban differences in cardio metabolic risk factors have largely disappeared and the risk factors are equal or slightly greater in rural subjects.

PATHOGENESIS

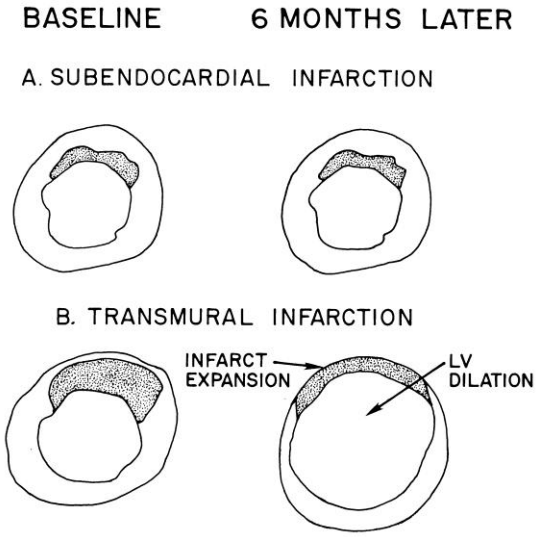
Thrombosis over plaques occurs due to two different processes. One by an extension of the process of endothelial denudation so that large part of the plaque are exposed. This process is known as endothelial erosion. The second mechanism for thrombus formation is plaque disruption. Here the plaque cap tears to expose the lipid core to blood in the arterial lumen. The core area is highly thrombogenic, containing tissue factor, fragments of collagen, and crystalline surfaces to accelerate coagulation. Thrombus forms initially in the plaque itself which is expanded and distorted from within; thrombus may then extend into the arterial lumen. The inflammatory process both reduces collagen synthesis by inhibiting the smooth muscle cell and causes its death by apoptosis[5].

Metalloproteinase production by macrophages is up regulated by inflammatory cytokines such as TNF(tumour necrosis factor) alpha. Disruption is the predominant cause (> 85%) of major coronary thrombi in white males with high plasma concentrations of low density lipoprotein (LDL), and low concentrations of high density lipoprotein (HDL). In contrast, in women endothelial erosion is responsible for around 50% of major thrombi. Disruption has an intraplaque component more resistant to fibrinolytic treatment, while in erosion the thrombus is more accessible.

Transmural regional acute myocardial infarction is caused by a coronary artery occlusion which develops over a relatively short time frame of a few hours and persists for at least 6–8 hours. The infarcted tissue is structurally suggestive of a homogenous entity - that is, all the myocardium involved died at around the same

time. Non-transmural regional infarcts (non-Q wave) have a different structure which is built up by the coalescence of many small areas of necrosis of very different ages.

This pattern of necrosis in crescendo unstable angina appears to be caused by repetitive episodes of short lived occlusion or platelet embolisation, or both. A further factor in limiting the spread of necrosis and preserving the subpericardial zone is the existence of prior collateral flow in the affected artery. Subjects with the highest concentrations of C reactive protein have the largest plaque mass[6].



Any factor which increases systemic inflammation would potentially trigger plaque instability and increase the risk of unstable angina. Systemic low grade inflammation include infection by chlamydia or helicobacter, rheumatoid arthritis. Current view of atherosclerosis is that primary stimulus is reaction between oxidised LDL and macrophage[7].

ISCHEMIC HEART DISEASE

Patients with ischemic heart disease are divided into two main groups those with stable angina and those with acute coronary syndrome.

Acute coronary syndrome are further divided into those with ST elevation myocardial infarction who are candidates for reperfusion therapy and those with unstable angina and non-ST elevation myocardial infarction[8] .

The incidence of unstable angina and non ST elevation myocardial ischemia is on the rise.

DEFINITION

Stable angina- Is characterized by chest or arm discomfort that may or may not be associated with pain but is reproducible with physical exertion or stress and is relieved within 5-10 minutes by rest or sublingual nitroglycerin.

Unstable angina- Is defined as angina pectoris or equivalent ischemic discomfort with at least one of three features:

1. It occurs at rest (or with minimal exertion), usually lasting >10 minutes
2. It is severe and of new onset (i.e., within the prior 4–6 weeks)
3. It occurs with a crescendo pattern (i.e., distinctly more severe, prolonged, or frequent than previously).

Classification of unstable angina

1-**New onset angina** – occurring only after heavy physical exertion have a prognosis similar to that of chronic stable angina, in contrast angina occurring with minimal exertion or at rest and which is prolonged caries a worse prognosis in the absence of intervention[9].

2-**Rest angina** - Prolonged angina and/or associated with transient ST segment changes >0.05 mV, identifies patients at increased risk.

3-**Early post MI angina**- Chest pain occurring within 48hrs after an acute MI. Is associated with persistent intracoronary thrombus , or severe coronary disease. The recurrent chest pain may indicate either viable myocardium in infarct zone or involvement of a new territory. Angina occurring after an acute MI has a high risk in the absence of intervention.

4- **Post revascularisation angina** – Angina after PCI(percutaneous coronary intervention) or CABG(coronary artery bypass grafting) may reflect a procedural event or restenosis or progression of native valve disease.

5- **Periprocedural angina**[10] – Ischemic chest pain within 48 hrs of stenting. It may be due to stent thrombosis, untreated dissection, transient coronary spasm or embolization.

Regardless of type, the risk is greatest with angina that is refractory to or occurs despite maximal medical therapy and with an accelerating tempo of ischemic symptoms in the preceding 48 hours (crescendo angina).

Braunwald classification of unstable angina [11]– Proposed in the year 1989 to facilitate the assignment of patients to a particular risk group. Patients with NSTEMI were included since troponins were not measured. It takes into account the severity of symptoms, the clinical circumstances surrounding the anginal episode, and the intensity of treatment.

Severity

- Class I — New onset, severe, or accelerated
- Class II — Angina at rest and subacute (no anginal episodes within (the preceding 48 hours)

- Class III — Angina at rest and acute (angina within the preceding 48 hours)

Clinical circumstances

- Class A — Secondary UA (in the setting of anemia, infection, fever, etc)
- Class B — Primary UA
- Class C — Post-MI angina

Intensity of treatment

- No or minimal treatment
- Symptoms occurring in the setting of standard medical therapy
- Symptoms occurring despite maximally tolerated doses of beta blockers, nitrates, and calcium channel blockers

NSTEMI – Patient with clinical features of unstable angina who develop evidence of myocardial necrosis in the form of elevated cardiac biomarkers. Previously the diagnosis of NSTEMI was defined by WHO as two of the following three criteria[12]:

1. Typical ischemic chest pain.
2. Typical ECG pattern including the development of Q waves.
3. Typical rise and fall in serum markers of myocardial injury, usually creatine kinase myocardial band (CK-MB).

With the introduction of serum troponins which were more specific and sensitive than CK-MB(creatine kinase myocardial band) levels,the following is the definition of an acute, evolving, or recent MI according to ACC(American College Of Cardiology).

TYPICAL RISE AND GRADUAL FALL OF SERUM TROPONIN LEVELS OR A MORE RAPID RISE AND FALL OF SERUM CK-MB LEVELS IN ADDITION TO PRESENTING WITH EITHER ISCHEMIC SYMPTOMS, DEVELOPMENT OF PATHOLOGIC Q WAVES ON ECG, ST-SEGMENT CHANGES INDICATIVE OF ISCHEMIA, OR CORONARY ARTERY INTERVENTION, EG PCI.

Patients presenting with NSTEMI have an intermediate risk of acute complications when compared to unstable angina (lower risk) and STEMI (higher risk) with a 30-day mortality rate of approximately 5 percent.

The clinical presentation of myocardial ischemia is acute chest discomfort[13]. The diagnosis of acute coronary syndrome depends on characteristic of pain, associated symptoms, ECG changes and biomarkers of cardiac injury. Clinical symptoms of typical cardiac pain include retrosternal chest pain with radiation to upper limbs or jaw or back with profuse sweating and vomiting.

Acute coronary syndrome is always caused by atherosclerosis with superimposed thrombosis. Genetic factors, a high-fat and energy-rich diet, smoking, and a sedentary lifestyle are associated with the emergence of IHD.

Obesity, insulin resistance, and type 2 diabetes mellitus are increasing and are powerful risk factors for IHD (ischemic heart disease). IHD primarily occurs in patients over the age of 40 years, younger men and women can also be affected. 40-45 years is used as a cut off to define young patients[14].

ECG CHANGES IN ISCHEMIC HEART DISEASE

ECG finding depend on following characteristics.

1) Duration - Hyper acute / acute , evolving / chronic
2) Size - Amount of myocardium affected
3) Localization - Anterior vs. inferior, posterior

Diagnosis is different in the presence of left bundle branch block.

ST segment is relatively isoelectric (flat along the baseline) under normal conditions[15]. During current of injury the ST segment is deviated from the baseline. The polarity and magnitude depends on the location and severity of injury.

Following are the criteria for diagnosis of ischemia

1. New ST elevation at the J-point in two contiguous leads that equals or exceeds 0.2 mV in men or 0.15 mV in women in leads V2-3 and/or 0.1mV in other leads[16].
2. New horizontal or down sloping ST segment depression equal to or greater than 0.05 mV in two contiguous leads.
3. T wave inversions equal to or greater than 0.1 mV in two contiguous leads with prominent R waves or an R/S ratio greater than 1.0.

MANAGEMENT IN ACUTE MYOCARDIAL INFARCTION

The first step in management is prompt recognition because early institution of revascularization therapy results in beneficial effect.

Once a diagnosis of MI is made the management involves

1) Relief of pain

2) Assessment of hemodynamic status and correction
3) Initiation of reperfusion either with fibrinolysis or primary coronary intervention
4) Antithrombotic therapy to prevent rethrombosis or stent thrombosis.
5) Beta blocker to prevent recurrent ischemia and arrhythmias.

This is followed by drugs that improve long term prognosis

1) Antiplatelet therapy to prevent recurrent thrombosis[17]
2) ACEI to prevent remodeling of left ventricle
3) Statin therapy
4) Anticoagulation in case of left ventricular thrombus or presence of atrial fibrillation.

Initial therapy

Supplemental oxygen - In patients with arterial saturation less than 90% or in patients with respiratory distress. In a normoxic individual it has been shown to produce a direct vasoconstrictor effect on coronary arteries[18].

Control of pain – Morphine 2 to 4 mg, intravenously with increments of 2 to 8 mg repeated at every 5 to 15 minute intervals.

Nitrates - Intravenous nitroglycerin is useful in patients with persistent chest pain after three sublingual nitroglycerin tablets, as well as in patients with hypertension or heart failure. Must be used with caution or avoided in settings in which hypotension is likely or could result in serious hemodynamic decompensation, such as right ventricular infarction or severe aortic stenosis.

Antiplatelet therapy - Including aspirin, P2Y12 receptor blocker and in patients undergoing primary PCI GP IIb/IIIa inhibitor improves outcomes.

Aspirin use within first 24 hours after acute STEMI improves outcome. There is a significant reduction in incidence of non-fatal reinfarction.

There was a 30 percent reduction in vascular events and an absolute benefit of 3.8 vascular events prevented per 100 patients at one month. The benefit of aspirin therapy in high-risk patients is independent of age, gender, or the presence of diabetes mellitus[19].

Dosing - An initial loading dose of 160-325 mg of uncoated aspirin should be given. It produces a rapid antithrombotic effect due to immediate and almost complete inhibition of thromboxane A2 production. Aspirin should be continued indefinitely at a dose of 75 to 162 mg/day. The long-term clinical benefit derived from aspirin appears to be relatively independent of dose.

In case of PCI with stenting aspirin 162 to 325 mg/day for at least one month in patients who received a bare metal stent (BMS), for three months in those who received a sirolimus-eluting stent (SES), and for six months for those who received a paclitaxel-eluting stent (PES)[20].

P2Y12 receptor blockers — The P2Y12 receptor blockers include **clopidogrel, ticlopidine, prasugrel, and ticagrelor.** Most evidence suggests that the benefits of these agents are additive to those of aspirin. The most important common side effect associated with therapy is bleeding.

The addition of the P2Y12 inhibitor clopidogrel to background treatment with aspirin to STEMI patients reduces the risk of clinical events (death, reinfarction and

stroke) and improves the patency of infarct related artery in patients receiving fibrinolytic therapy.

New P2Y12 ADP receptor antagonists, such as prasugrel and ticagrelor, are more effective than clopidogrel in preventing ischemic complications in STEMI patients undergoing PCI.

Dosing – Compared to 300mg loading dose, the 600 mg loading dose appears to produce maximal antiplatelet activity within two to three hours, to have a greater antiplatelet effect, to diminish the likelihood of clopidogrel resistance. Treat patients not at high risk for bleeding for one week with the higher maintenance dose of clopidogrel 150 mg. After one week the maintenance dose is 75 mg daily.

The preferred ADP-receptor blockers are prasugrel [60 mg (p.o.) loading dose, 10 mg maintenance dose] or ticagrelor [180 mg p.o. loading dose, 90 mg maintenance dose][21].

Prasugrel was found to be more effective than clopidogrel in reducing composite primary endpoint (cardiovascular death, non-fatal MI, or stroke) in clopidogrel-naive patients undergoing PCI, either primary or secondary PCI for STEMI, or moderate to high-risk non-ST-segment elevation acute coronary syndromes (NSTE-ACS) once coronary angiography had been performed with a significant increase in rate of bleeding.

Prasugrel is contraindicated in patients with prior stroke/transient ischaemic attack (TIA). Its use is generally not recommended in patients aged ≥75 years or in patients with lower body weight (<60 kg). Prasugrel is used only in cathlab for planned PCI. Is not used in emergency department or in medically treated patients.

Ticagrelor also reduced the composite end point and cardiovascular mortality with no significant increase in bleeding risk .Prasugrel and ticagrelor should not be used in patients with a previous haemorrhagic stroke or in patients with a moderate-to-severe liver disease. Is recommended in patients with moderate to high risk of ischemic events regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued after ticagrelor is started.

Glycoprotein IIb/IIIa inhibitors - Platelet activation by thrombin and other agonists can bypass the arachidonic acid-thromboxane pathway to directly stimulate platelet aggregation via the glycoprotein (GP) IIb/IIIa receptor on the platelet surface. In animal models inhibition of the GP IIb/IIIa receptor accelerated thrombolytic recanalization of thrombosed coronary arteries and prevented cyclical reflow and reocclusion.

Use of GP IIb/IIIa inhibitors is indicated in patients with STEMI who undergo primary PCI and are treated with unfractionated heparin. Drugs used are abciximab, tirofiban , eptifibatide[22].

The very high local platelet inhibitor concentration associated with intracoronary delivery of GP IIb/IIIa inhibitors has the potential to dissolve thrombi and microemboli and to impair further clot formation to a greater extent than intravenous delivery.

Fibrinolytic therapy - Fibrinolysis is an important reperfusion strategy, where primary PCI cannot be offered to STEMI patients within the recommended timelines. The benefit of fibrinolytic therapy in STEMI is well established. 30 early deaths are prevented per 1000 patients treated within first 6 hours of symptom onset. The benefit

is also seen in patients over the age of 75 years who present within 12 hours of symptom onset and significantly reduces the mortality rate[23].

Fibrinolytic therapy is a proven treatment for the management of AMI. It is more universally available to patients without contraindications, can be administered by any properly trained health care provider, and can be given in the prehospital setting. Its efficacy declines as the duration of ischemia increases. The goal is a door-to-needle time of less than 30 minutes, and every effort must be made to minimize the time to therapy. Patients older than 75 years derive significant benefit from fibrinolytic therapy, even though their risk of bleeding is higher.

Time to treatment

A greater mortality reduction was noted when thrombolysis was performed within first 2 hours than in those treated after that.In case of pre hospital fibrinolysis the outcome is similar to that of PCI[24].

Absolute contraindications for fibrinolytic use in STEMI include the following:

- Prior intracranial hemorrhage (ICH)
- Known structural cerebral vascular lesion
- Known malignant intracranial neoplasm
- Ischemic stroke within 3 months
- Suspected aortic dissection
- Active bleeding or bleeding diathesis (excluding menses)
- Significant closed head trauma or facial trauma within 3 months
- Intracranial or intraspinal surgery within 2 months

- Severe uncontrolled hypertension (unresponsive to emergency therapy)
- For streptokinase, prior treatment within the previous 6 months

Relative contraindications for fibrinolytic use in STEMI include the following:

- History of chronic, severe, poorly controlled hypertension
- Significant hypertension on presentation (systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg
- Traumatic or prolonged (>10 minutes) cardiopulmonary resuscitation (CPR) or major surgery less than 3 weeks previously
- History of prior ischemic stroke not within the last 3 months
- Dementia
- Recent (within 2-4 weeks) internal bleeding
- Noncompressible vascular punctures
- Pregnancy
- Active peptic ulcer
- Current use of an anticoagulant (eg, warfarin sodium) that has produced an elevated international normalized ratio (INR) higher than 1.7 or a prothrombin time (PT) longer than 15 seconds

THROMBOLYTIC REGIMENS

Alteplase

Alteplase can be administered in an accelerated infusion (1.5 hr) using 50-mg and 100-mg vials reconstituted with sterile water to 1 mg/mL. Accelerated infusion of alteplase for AMI consists of a 15-mg IV bolus followed by 0.75 mg/kg (up to 50 mg)

IV over 30 minutes and then 0.5 mg/kg (up to 35 mg) IV over 60 minutes[25]. The maximum total dose is 100 mg for patients weighing more than 67 kg. This is the most common alteplase infusion parameter used for AMI.

Reteplase

First, reconstitute two 10-unit vials with sterile water (10 mL) to 1 U/mL. The adult dose of reteplase for AMI consists of two IV boluses of 10 units each; there is no weight adjustment. The first 10-unit IV bolus is given over 2 minutes; 30 minutes later, a second 10-unit IV bolus is given over 2 minutes. Administer normal saline (NS) flush before and after each bolus.

Tenecteplase

To reconstitute tenecteplase, mix the 50-mg vial in 10 mL sterile water (5 mg/mL). Tenecteplase is administered in a 30-50 mg IV bolus over 5 seconds. The dosage is calculated on the basis of the patient's weight, as follows:

- <60 kg - 30 mg (6 mL)
- 60 to 69 kg - 35 mg (7 mL)
- 70 to 79 kg - 40 mg (8 mL)
- 80 to 89 kg - 45 mg (9 mL)
- ≥90 kg - 50 mg (10 mL)

Streptokinase

The adult dose of streptokinase for AMI is 1.5 million U in 50 mL of 5% dextrose in water (D5W) given IV over 60 minutes. Allergic reactions force the termination of many infusions before a therapeutic dose can be administered.

Complications – Fibrinolysis is associated with small but significant increase in risk of strokes. Early strokes are due to hemorrhage and later are due to thrombosis or emboli. Advanced age, female gender, previous cerebro vascular disease, systolic and diastolic hypertension at the time of admission is predictors of intracranial hemorrhage. Admission of streptokinase is associated with hypotension and rarely allergic reactions.

STREPTOKINASE – Was discovered by William Smith Tillett in 1933. First used to treat fibrinous, purulent, and sanguineous pleural exudations, hemothorax and tuberculous meningitis. The streptococcal substance (fibrinolysin) activates the proteinase precursor converting it to an active enzyme in a manner analogous to the conversion of trypsinogen to trypsin by enterokinase[26]. The active serum proteinase then lyses the fibrin clot. Christensen and MacLeod proposed the term "streptokinase" in 1945 to replace the term fibrinolysin originally applied to the streptococcal component. Till 1980s the use of streptokinase was not widespread. After successful experiments in animals, Boucek and Murphy used streptokinase in human beings. They injected streptokinase into the coronary sinus (catheterized via the right brachial artery) in patients who had coronary occlusion as detected by electrocardiography.

In the landmark GISSI trial established the efficacy of streptokinase in acute STEMI, the sooner a patient was admitted to a coronary care unit and streptokinase was administered, the better are the chances of recovery. Commercial streptokinase used for thrombolytic therapy is derived from S.equisimilis (Lancefield Group C).

Worldwide streptokinase is the most widely used fibrinolytic agent for acute myocardial infarction. Complete early reperfusion is achieved only in one third of patients.

Dose of streptokinase is 1.5 million units infusion in 30-60 minutes. 90 minute patency rate is around 50%.

Fibrinolytic therapy is indicated in patients with STEMI who presents within 12 hours of symptom onset has no contraindications for fibrinolysis and presents to a facility without the capability for expert, prompt intervention with primary PCI within 90 minutes of first medical contact.

First patient contact to initiation of fibrinolytic drug infusion time period should be less than 30 minutes.

Fibrinolytic therapy does not improve outcomes in patients presenting after 12 hours of symptom onset and is not indicated who are stable and pain free. But fibrinolysis can be considered for upto 24 hours in patients presenting with ongoing chest pain and non-availability of PCI.

Primary percutaneous intervention- Is defined as an emergent percutaneous catheter intervention. PCI has enhanced survival as compared to fibrinolysis and also has a low rate of intracranial hemorrhage and recurrent myocardial infarction. The ACC/AHA guidelines recommend the use of primary PCI in acute STEMI who can undergo the procedure within 90 minutes of first medical contact by persons skilled in the procedure[27].

For patients with STEMI, immediate coronary angiography with PCI is recommended (primary PCI).

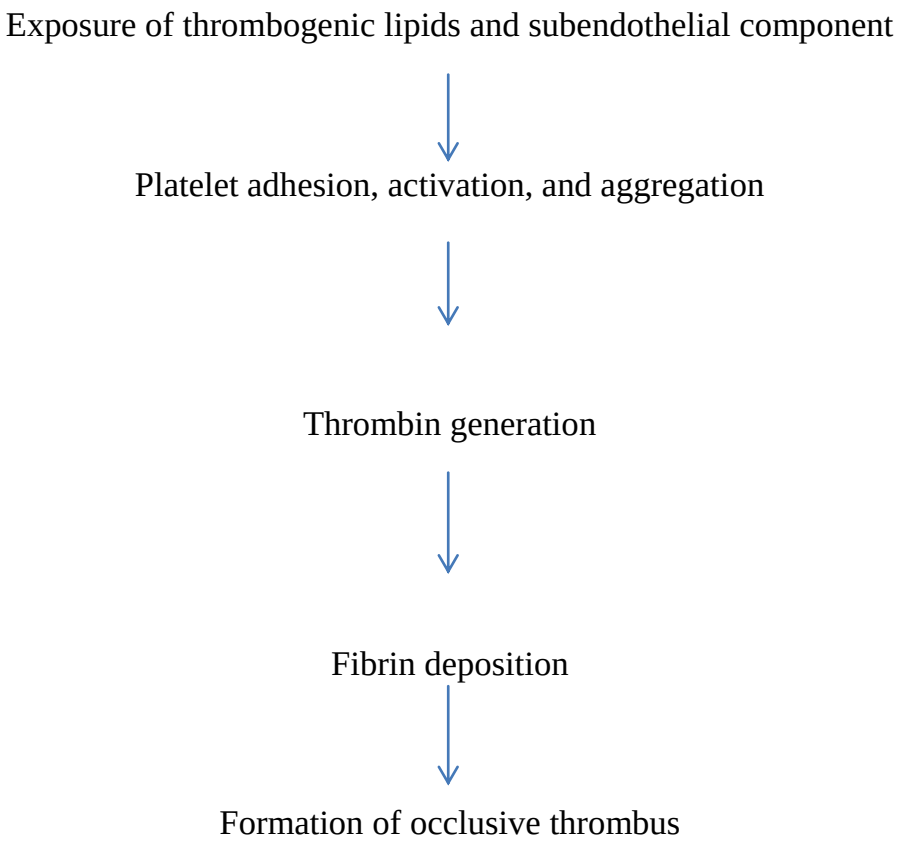
For patients with NSTE-ACS, American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines on the management of NSTE-ACS (updated in 2014) recommend an early invasive strategy in most cases, with timing as follows:

- Immediate (within 2 hours) - Patients with refractory angina, recurrent angina after initial treatment, signs/symptoms of heart failure, new/worsening mitral regurgitation, hemodynamic instability, sustained ventricular tachycardia, or ventricular fibrillation.
- Early (within 24 hours) - None of the immediate characteristics but new ST-segment depression, a GRACE risk score >140, or temporal change in troponin.
- Delayed invasive (within 25-72 hours) - None of the immediate or early characteristics but renal insufficiency (glomerular filtration rate [GFR] <60 mL/min/1.73 m^2), left ventricular ejection fraction (LVEF) <40%, early postinfarct angina, history of PCI within the preceding 6 months, prior CABG, GRACE risk score of 109-140, or TIMI score of 2 or higher.

Skilled PCI is defined as a Centre that performs more than 200 PCI per year of which 36 are primary and has experienced operators performing more than 75 cases per year and has cardiac surgery capability. 50% of patients with STEMI have multi vessel disease[28]. Only the infarct related artery should be treated during the initial intervention. The exception are cardiogenic shock critical stenosis more than 90% highly unstable lesions and persistent ischemia after PCI of culprit lesion.

ANTICOAGULATION AFTER THROMBOLYSIS

Rupture of atheromatous plaque leads to thrombus formation in the following way



Thrombin activity at site of rupture results in delayed or incomplete reperfusion leading to reocclusion. Therefore patency of infarct related vessel after fibrinolysis reduces adverse outcomes. Thrombin is central mediator of clot formation by activating platelets, conversion of fibrinogen to fibrin activates factor thirteen leading to fibrin cross linking and stabilization of clot[29]. Thrombin molecules bound to intramural thrombus are exposed during endogenous and exogenous fibrinolysis,

also in addition thrombin is generated directly and indirectly by fibrinolytic agents by activation by plasmin of prothrombin and factors V and X.

Experimental models have demonstrated that concurrent thrombin inhibition enhances coronary fibrinolysis and prevents reoclussion.

UFH appears to markedly attenuate the thrombin activity associated with fibrinolysis and prevent early recurrent coronary thrombosis. Heparin interacts with antithrombin-III greatly increasing its inhibitory effects on thrombin. The heparin-antithrombin-III complex also inhibits factor Xa and other clotting factors. Use of concurrent heparin therapy decreases early thrombin activity and improves patency of culprit artery and prevents reocclusion.The use of heparin after thrombolysis was indicated in case of fibrin specific agents but with streptokinase it was controversial. But recent studies have shown clear benefit of anticoagulation after thrombolysis with streptokinase, that antithrombins at least potentiate non fibrin specific fibrinolysis when compared with no anticoagulation.

Regarding the time of anticoagulation and intensity of anticoagulation one study performed by GUSTO I trial found that optimal level of anticoagulation is to maintain an APTT in the range of 50-70 seconds for 48 hours which reduces the incidence of reinfarction and maintains the patency of infarct related artery[30]. In GUSTO I trial all patients were anticoagulated at the end of 6 hours. In one study done by Jef Arnout et al they found that after thrombolysis with alteplase concomitant heparinisation was given and found that patients who were heparinized earlier maintained a better infarct related artery patency.

PHARMACOLOGIC ANTICOAGULATION THERAPY

Unfractionated heaprins

A study by Oler et al found that unfractionated heparin was associated with a 33% reduction in the risk of myocardial infarction or death in patients with unstable angina who were treated with aspirin plus heparin, compared with patients who were treated with aspirin alone[31]. The FUTURA/OASIS-8 randomized trial found that low-dose unfractionated heparin, 50 U/kg (regardless of use of glycoprotein IIb/IIIa inhibitors), compared with standard-dose unfractionated heparin, 85 U/kg (60 U/kg with Gp IIb/IIIa inhibitors), did not reduce major peri-PCI bleeding and vascular access-site complications.

Action of heparin :

Heparins are indirect thrombin inhibitors that complex with antithrombin and convert antithrombin from a slow to a rapid inactivator, a proteolytic enzyme that inactivates factor IIa (thrombin), factor IXa, and factor Xa. UFH prevents thrombus formation but is inactive against clot bound thrombin. LMWHs are relatively more potent inhibitors of factor Xa than of thrombin. Compared to UFH, LMWH has decreased nonspecific binding, a longer half-life, and predictable anticoagulation, permitting once- or twice-daily subcutaneous administration. LMWH does not require lab monitoring.

Adjuvant anticoagulant therapy gives improvement in coronary artery patency as like antiplatelet therapy. The additional benefits include prevention of deep vein thrombosis prevention of left ventricular thrombus and pulmonary embolism.

Two recent studies have demonstrated the benefit of anticoagulation after thrombolysis with streptokinase[32]. The typical regimen for use in STEMI is an initial bolus of 60 U/kg (max 4000 U) and continued as an infusion of 12 U/kg/hr (max 1000 U/hr) for 48 hours adjusted to achieve an APTT of 50–70 seconds. A typical drawback of UFH is significant variability in response.

It is very difficult to achieve and maintain a target of APTT within this range and under treatment is a major problem. In the TIMI 9b trial only one third of patients had APTT within this range. Once the APTT exceeds above 70secs the risk of intracranial hemorrhage increases significantly.

Low–molecular-weight heparin

LMWHs might be superior to unfractionated heparin in reducing cardiovascular outcomes, with a safety profile similar to that of heparin in patients receiving medical care.

Conflicting results emerged from 9 randomized trials directly comparing LMWH with unfractionated heparin. Two trials evaluated dalteparin, another evaluated nadroparin, and 6 evaluated enoxaparin. Trials with dalteparin and nadroparin reported similar rates of nonfatal myocardial infarction or death compared with heparin, whereas 5 of 6 trials of enoxaparin found point estimates for death or nonfatal myocardial infarction that favored enoxaparin over heparin. The benefit of enoxaparin appeared to be driven largely by a reduction in nonfatal myocardial infarction, especially in the cohort of patients who had not received any open-label anticoagulant therapy before randomization.

In addition, a systematic review comparing LMWH with unfractionated heparin found no significant difference in benefits between the 2 drugs.

Aside from the possible medical benefits of using LMWH in place of unfractionated heparin, advantages of LMWH include ease of administration, absence of need for anticoagulation monitoring, and potential for overall cost savings. Although 3 LMWHs are approved for use in the United States, only enoxaparin is currently approved for use in unstable angina. Lev et al found that the combination of eptifibatide with enoxaparin appears to have a more potent antithrombotic effect than that of eptifibatide and unfractionated heparin.

The role of LMWHs in patients for whom PCI is scheduled is relatively ill defined. However, it is likely to be at least equivalent to that of heparin. It appears reasonable to minimize the risk of excessive anticoagulation during PCI by avoiding crossover of anticoagulants (ie, maintain consistent anticoagulant therapy from the pre-PCI phase throughout the procedure itself). Additional experience with regard to the safety and efficacy of the concomitant administration of LMWHs with Gp IIb/IIIa antagonists and fibrinolytic agents is currently being acquired[33].

Adding apixaban (5 mg twice daily) to antiplatelet therapy in high-risk patients after ACS may increase the number of major bleeding events without significantly reducing recurrent ischemic events.

Factor Xa inhibitors

Interestingly, thrombin generation remains elevated up to 6 months after an ACS episode.6 Specifically, these initial 6 months post-ACS is when most of the recurrent events take place according to GUSTO Registry ACS.7 Therefore, inhibition

of thrombin generation seems a rational therapeutic target in the treatment of ACS. Two major observations support the notion that a more effective antithrombotic therapy may reduce recurrent ACS events: (i) a meta-analysis of 10 trials and 5938 patients showed a 44% reduction in recurrent myocardial infarction (MI) by warfarin (which also reduces Xa) + ASA when compared with ASA monotherapy;8 (ii) fondaparinux, an indirect Xa inhibitor, has also showed benefits in the treatment of ACS9,10 (although these studies only included acute administration of fondaparinux).

Oral Xa inhibitors are novel anticoagulants overcoming many of the disadvantages of warfarin (numerous food and drug interactions, narrow therapeutic window, variable dose–response relationship, need for frequent monitoring), thus offering a new treatment strategy in patients with ACS. In the present article, we review the current evidence for the addition of novel Xa inhibitors to antiplatelet therapy in the context of ACS[34].

Rivaroxaban is another highly selective, reversible, oral direct factor Xa inhibitor capable of inhibiting both free factor Xa and factor Xa bound in the prothrombinase complex. It can be administered once daily,17 a great improvement for patient compliance. Rivaroxaban is not recommended in patients with creatinine clearance (CrCl) , 15 mL/min and it should be used with caution in patients with CrCl 15–29 mL/min.

In an initial meta-analysis28 combining the seven randomized controlled trials (RCTs) with new anticoagulants (APPRAISE 1 and 2 for apixaban, ATLAS TIMI 46 and TIM 51 for rivaroxaban, RUBY for darexaban, REDEEM for dabigatran, and ESTEEM for ximelagatran), the authors show that the use of new-generation oral

anticoagulant agents after ACS was associated with a dramatic increase in major bleeding events [odds ratio (OR) 3.03 (2.20–4.16), P ¼ 0.001], and with significant but moderate reductions in the risk for stent thrombosis or ischaemic events [OR 0.86 (0.79–0.94), P ¼ 0.001], without a significant effect on overall mortality [OR 0.9 (0.76–1.06), P ¼ 0.22]. For the net clinical benefit, new-generation oral anticoagulant agents provided no advantage over placebo [OR 0.98 (0.90– 1.06), P ¼ 0.57][35]. These results have been recently con- firmed by a second independent meta-analysis.29 The most recent meta-analysis exclusively analyses the five RCTs performed with Xa inhibitors30 and has also con- firmed the previous results. There was no significant difference in mortality between patients treated with Xa inhibitors vs. those receiving the standard therapy [OR 0.97 (0.72–1.31), P ¼ 0.86]. As shown in the previous meta-analyses, recurrent MI rates were decreased in the anti-Xa group [OR 0.86 (0.76–0.98), P ¼ 0.02, number needed to treat ¼ 189] at the expense of an increased risk of major bleedings [OR 3.24 (2.29–4.59), P ¼ 0.001, number needed to harm ¼ 104]. Therefore, the addition of the new oral anticoagulants on top of standard therapy seems to result in an excessive risk of major bleeding without any clear evidence of outweighting clinical benefits.

Following an ACS, patients remain at increased risk of recurrent ischaemic events, despite optimal DAPTand revascularization. Treatment targeted towards thrombinmediated pathways of platelet aggregation and activation offer an attractive therapeutic target in minimizing such adverse events, as thrombin abundance characterizes the cellular milieu in the immediate period after ACS. Results to date have been mixed as some studies have demonstrated significant increases in bleeding

risk without improvements in clinical outcomes when used in conjunction with DAPT. Of the currently available antithrombotics, only the direct Xa inhibitor rivaroxaban appear to hold the most promise in the management of patients with recent ACS, although the burden of missing data in the ATLAS-TIMI 51 trial requires some caution when analysing its results.

ROLE OF HEPARIN IN CORONARY THROMBOLYSIS

Although the benefits of coronary thrombolysis are well established, the optimal therapeutic strategy for ensuring rapid and sustained coronary artery patency remains controversial.The available data suggest that the success of coronary thrombolysis depends not only on the induction of clot lysis, but also on the extent to which procoagulant activity that promotes recurrent thrombosis is inhibited [36]. Procoagulant activity increases almost immediately in patients treated with fibrinolytic agents, and persistent increases in thrombin activity have been associated with recurrent coronary thrombosis. Heparin administered intravenously appears to markedly attenuate the thrombin activity associated with thrombolysis and, in patients treated with tissue plasminogen activator (t-PA), prevents early recurrent coronary thrombosis.

The results of clinical trials of coronary thrombolysis indicate that conjunctive treatment of patients with heparin improves survival compared with treatment with fibrinolytic agents alone. Although recent clinical trials in which patients were treated with streptokinase suggested that 12,500 units of heparin administered subcutaneously twice daily decreases mortality, this dosage regimen does not induce therapeutic levels of anticoagulation within the 6rst 24 h in most patients. The failure to achieve early

therapeutic anticoagulation may account for the lack of mortality benefit in trials in which patients given t-PA were treated with conjunctive subcutaneous heparin therapy. Thus, the available experimental and clinical data suggest that intravenous heparin should be given to patients treated with fibrinolytic agents for acute myocardial infarction.

CLINICAL EVIDENCE THAT PROCOAGULANT ACTIVITY INCREASES DURING THROMBOLYSIS

Despite induction of intense fibrinolytic activity during coronary thrombolysis, recurrent coronary thrombosis often occurs. Even during administration of the fibrinolytic agent, episodes of transient reperfusion followed by reocclusion often precede sustained coronary reperfusion. Thus, the apparent failure to achieve sustained reperfusion may reflect the early or almost immediate recurrence of thrombosis[37]. The factors responsible for the recurrent thrombosis during coronary thrombolysis likely include the procoagulant activity of the residual thrombus-" or that induced by exposure of procoagulant factors in subendothelium of the underlying injured arterial wall or by activation of the fibrinolytic system. Although the specific mechanisms have not been defined, results of several clinical studies indicate that the persistence of increased thrombin activity in patients given fibrinolytic agents correlates with failure of therapy Increases in the plasma concentration of fibrinopeptide A (FPA),a marker of thrombin activity, have been documented in patients given t-PA or streptokinase for acute myocardial infarction.

Fibrinopeptide A is a small peptide cleaved by thrombin from fibrinogen when fibrin is formed. Fibrinopeptide A has a halflife in plasma of 3 to 5 min." Thus, elevations of the concentration of this peptide in plasma reflect ongoing thrombin activity. In patients given streptokinase without conjunctive heparin, plasma concentrations of FPA were found to increase in those in whom reperfusion did not occur and in those in whom reocclusion followed initial reperfusion[38].In the group with recurrent thrombosis, plasma concentrations of FPA remained elevated despite intravenous administration of heparin. Similar results were reported by Rapold et al'" in patients given t-PA for acute myocardial infarction. Persistent elevations of FPA, despite intravenous heparin, in patients treated with t-PA were also associated with recurrent coronary thrombosis in that study. These results indicate that thrombin activity increases during coronary thrombolysis in patients who are not treated with concurrent intravenous heparin, and that the extent of persistent thrombin activity appears to be an important determinant of the failure of therapy

Conjunctive administration of heparin appears to attenuate increases in thrombin activity, judging from studies showing less marked elevations in concentrations of FPA in plasma of patients given t-PA or streptokinase after an intravenous bolus of 5,000 units of heparin compared with results in patients given these agents without intravenous heparin.The increased levels of FPA observed in patients treated with t-PA or streptokinase but not given heparin initially decrease promptly after patients are given a bolus of intravenous heparin[39]. The prompt response to heparin is consistent with the increases in FPA being due to activity of thrombin at intravascular sites. Recently, Gulba et al characterized plasma

concentrations of thrombin-antithrombin III complexes, another marker of procoagulant activity, in patients treated with coronary thrombolysis. As opposed to plasma concentrations of FPA, which reflect thrombin activity, concentrations of thrombin-antithrombin III complexes reflect elaboration of thrombin and the quantity of thrombin inhibited by antithrombin III.

The results of the study by Golba et aI are similar to those of earlier studies of FPA: in patients treated with urokinase or t-PA, thrombin-antithrombin III complex levels increase in those in whom reperfusion is not achieved and in those who suffer reocclusion. The results of clinical studies characterizing procoagulant activity during coronary thrombolysis have consistently demonstrated that increases in thrombin activity occur in patients given fibrinolytic agents.[40]

Persistent increases in thrombin activity are associated with failure of thrombolysis to induce sustained re- perfusion. Administration of intravenous heparin appears to markedly attenuate the thrombin activity induced, but judging from the data of Owen et al, in which FPA elevations were documented despite heparin, it is likely that ongoing thrombin activity may occur at sites relatively protected from inhibition by heparin-antithrombin III. Thus, coronary thrombolysis is a dynamic process in which there is a balance between precoagulant activity, which promotes recurrent thrombosis, and fibrinolytic activity, which induces clot lysis[41].

POTENTIAL MECHANISMS FOR INCREASED PROCOAGULANT ACTIVITY DURING THROMBOLYSIS AND IMPLICATIONS FOR THE EFFICACY OF HEPARIN

Although the results of clinical studies indicate that procoagulant activity increases in patients treated With fibrinolytic agents, the mechanisms responsible are not well defined. In patients treated with t-PA or streptokinase, plasma concentrations of FPA increase almost immediately on infusion of the fibrinolytic agent[42]. Such increases are markedly attenuated, but not eliminated, by administration of intravenous heparin. Recent experimental studies suggest that pharmacologic activation of plasminogen may induce plasmin-mediated activation of the coagulation system. Incubation of nonanticoagulated blood with pharmacologic concentrations of streptokinase or t-PA induces marked thrombin activity, judging from the rapid increase in the concentration of FPA. Heparin is effective in inhibiting the procoagulant activity induced by plasmin, but concentrations higher than those typically achieved during intravenous therapy are required; The amount of thrombin activity induced appears to be directly related to the extent of free plasmin activity, so that agents, such as streptokinase, that induce extensive plasmin activity are associated with more marked procoagulant effects compared with fibrin-specific agents, such as t-PA, which induce less activation of plasminogen in plasma.In addition, plasmin induces activation of factor V, a cofactor that, when activated, increases the activity of the factor XalVa complex, which induces the formation of thrombin.

These observations suggest that plasmin-mediated activation of the coagulation system may account for the rapid increases in thrombin activity observed in patients given fibrinolytic agents. These procoagulant effects of pharmacologic thrombolysis appear to be attenuated by high therapeutic concentrations of heparin, providing a theoretic basis for initiation of intravenous heparin before administration of the fibrinolytic agent[43]. In addition to plasmin-mediated effects on procoagulant activity, recent data suggest that other mechanisms for recurrent thrombosis are likely in patients treated with coronary thrombolysis.

The procoagulant properties of the residual thrombus and high-grade stenosis that are present after coronary thrombolysis are potent stimuli for recurrent thrombosis. Although several factors appear to contribute to the procoagulant properties of the residual arterial thrombus, the activity of thrombin bound to fibrin may be the most important. Thrombin bound to fibrin retains its catalytic activity, and therefore will induce fibrin deposition and platelet activation. In addition, thrombin activates factors V and VIII, cofactors that, when activated, promote activation of the coagulation system .Because the thrombin activity associated with a thrombus appears to induce relatively little fibrin formation, it is likely that the secondary activation of factors V and VIII and the activation of platelets are the predominant mechanisms by which clot-associated thrombin activity induces recurrent thrombosis.

Thrombin bound to fibrin appears to be relatively protected from the inhibitory effects of heparin antithrombin III. In contrast, agents that inhibit the thrombin active site directly, such as D-phe-proarg- chloromethylketone, are equally effective in inhibiting fibrin-bound and free thrombin[44]. In nonhuman primates, this inhibitor

prevents platelet and fibrin deposition on Dacron vascular grafts in a model of arterial thrombosis. Recombinant hirudin, another potent thrombin inhibitor, has been shown to prevent platelet-rich arterial thrombosis in response to deep arterial wall injury and to prevent recurrent thrombosis in a canine model of coronary thrombolysis. In the thrombolysis preparation, hirudin also significantly accelerated the rate of clot lysis compared with that which occurred with conjunctive treatment with heparin or aspirin.

Although the results of recent experimental studies suggest that potent thrombin-specific inhibitors may be more active than heparin in preventing recurrent thrombosis after coronary thrombolysis, heparin is likely to be of clinical value. As opposed to thrombinspecific inhibitors, heparin-antithrombin III has inhibitory effects on factors other than thrombin, including IXa, Xa, and XIa. Thus, adequate concentrations of heparin may attenuate activation of the coagulation system by inhibiting the activity of factors other than thrombin. In addition, the relative lack of efficacy of heparin in experimental models may reflect properties specific to the manner in which thrombosis is induced in the model. In most instances, the experimental preparations are designed to induce extensive arterial wall injury in which fresh thrombus containing relatively large quantities of thrombin is formed. In contrast, coronary thrombosis in response to atherosclerotic plaque rupture may be associated with less thrombin activity, while the role of other procoagulants, such as tissue factor, may be more important. Nonetheless, the results of these studies have been of considerable value in emphasizing the importance of persistent thrombin activity as a determinant of recurrent thrombosis after coronary thrombolysis.[45]

CLINICAL EVIDENCE OF THE IMPORTANCE OF CONJUNCTIVE HEPARIN THERAPY WITH CORONARY THROMBOLYSIS .

Three recent trials have shown that coronary artery patency rates are significantly increased in patients who are given conjunctive intravenous heparin therapy with t-PA (alteplase) compared with patients given t-PAeither with no conjunctive therapy or with aspirin alone." Bleich et al" found that coronary artery patency was 71% in patients given heparin (n= 42) at 57 h compared with only 43% in patients not given heparin (n = 41) . In this trial, patients in the control group were not given aspirin. In the Heparin Aspirin Reperfusion Trial, patients were randomly assigned to intravenous heparin, titrated to maintain the activated partial thromboplastin time at 1.5 to 2.0 times control, or aspirin (80 mg/d) . Coronary artery patency was assessed at a mean of 18 h after the onset of treatment[46]. In patients treated with heparin (n=106), patency was 82%, compared with 52% in those who received only aspirin (n = 99). The results of the European Cooperative Study Group trial comparing treatment with conjunctive intravenous heparin and aspirin to treatment with aspirin alone are consistentwith the results of these earlier trials; coronary artery patency was demonstrated in 83% of patients given heparin and aspirin, compared with 75% of those treated with aspirin alone . Unfortunately, the sample sizes of these trials are inadequate to allow assessment of whether there is a mortality benefit associated with the higher rate of patency in patients given conjunctive intravenous heparin treatment with t-PA. Nonetheless, an analysis of pooled data from trials with fibrinolytic agents suggests that early mortality is decreased in patients who are given conjunctive heparin treatment with coronary

thrombolysis. The value of conjunctive intravenous heparin therapy in patients treated with streptokinase, urokinase, or anisoylated plasminogen streptokinase activator complex (APSAC) has not been established by randomized clinical trials. Nonetheless, there is clinical evidence that streptokinase and urokinase induce marked procoagulant activity, judging from the elevations in plasma concentrations of FPA and thrombin-antithrombin III complexes.: Heparin appears to attenuate markedly, although not completely prevent; the thrombin activity induced by streptokinase. However, the marked decreases in the concentration of clottable fibrinogen in patients treated with streptokinase or urokinase and the inhibitory effects of fibrinogen degradation products on fibrin polymerization and platelet aggregation may attenuate recurrent thrombosis, particularly early after administration of the agent.[47]

Although comparative studies including conjunctive intravenous heparin are lacking, several trials have compared mortality in patients treated with coronary thrombolysis with or without high-dose subcutaneous heparin (12,500 units given twice daily) started at various intervals after administration of the fibrinolytic agent. In the Studio sulla Calciparina nell'Angina e nella Thrombosi Ventriculare nell'Infarto (SCATI) trial,36 patients were given either a 2,OOO-unit intravenous bolus of heparin followed by 12,500 units subcutaneously every 12 h or no anticoagulant therapy In a nonrandomized subset of SCATI patients given streptokinase within 6 h of the onset of symptoms, mortality was lower in the patients treated with heparin than in those not treated with an anticoagulant (4.5% compared with 8.8%).36 There was also a trend toward decreased mortality in the Second International Study ·of Infarct Survival (ISIS-2) in patients randomly assigned to treatment with streptokinase with or without

aspirin, in whom treatment with heparin was "planned at entry." In ISIS-2, however, the decision whether to treat with heparin and the mode of heparin administration *(ie,* subcutaneous or intravenous) was made in a nonrandomized manner by the treating physician. A trend toward lower mortality in patients randomly assigned to treatment . with streptokinase and high-dose subcutaneous heparin (7.2%), compared with that in patients given streptokinase alone (9.2%), was also noted in the Gruppo Italiano per 10 Studio della Sopravvivenza nell'Infarto miocardico (GISSI)-III International Study Group trial. This finding may have been due to chance alone, because a difference in mortality existed between these two groups before heparin was initiated. Preliminary results of the Third International Study of Infarct Survival (ISIS-3) apparently indicate a mortality benefit (5 lives saved per 1,000 patients) with treatment with high-dose subcutaneous heparin started 4 h after administration of t-PA (duteplase), APSAC, or streptokinase. Thus, the results of several large clinical trials suggest that treatment with high-dose subcutaneous heparin may decrease mortality in patients treated with streptokinase, but not in patients treated with t-PA. These results are not consistent with the data indicating that the rate of coronary artery patency is significantly decreased in patients treated with t-PA without conjunctive intravenous heparin[48].

One interpretation of this discrepancy is that early coronary artery patency is not the primary detenninant of mortality in patients treated with fibrinolytic agents for myocardial infarction. This view is inconsistent with the data indicating that the greatest mortality reduction in patients with myocardial infarction treated with fibrinolytic agents occurs in those treated within the first hour of symptoms,and that the benefit of thrombolysis decreases in patients treated more than 4 h after symptom

onset. The importance of early patency is also supported by preliminary data from a recent trial documenting a higher 9O-min patency rate in patients given t-PA than in those given APSAC,39 which was associated with improved survival in the t-PA groUp. Of note, all patients in this study were treated with conjunctive intravenous heparin. Although other mechanisms may contribute to the reduction of mortality in patients given fibrinolytic agents for acute myocardial infarction, considerable clinical and experimental evidence suggests that early and sustained recanalization of the infarct-related artery is essential for maximal benefit to occur.

CLINICAL PHARMACOLOGY OF CONJUNCTIVE HEPARIN THERAPY

An important consideration in interpreting the results of recent clinical trials with regard to the role of conjunctive heparin therapy is the marked differences in the extent and rapidity of anticoagulation achieved with intravenous compared with subcutaneous heparin. Intravenous administration of heparin initiated with a 5,OOO-unit intravenous bolus followed by a continuous infusion of approximately 30,000 units over 24 h results in therapeutic heparin levels in most patients within the first 24 h. In contrast, Turpie et al reported that heparin levels are not in the therapeutic range during the first 24 h in patients with acute myocardial infarction who are treated with Thus, even high doses of subcutaneous heparin given conjunctively with fibrinolytic agents are unlikely to induce sufficient therapeutic levels of anticoagulant activity within the first 24 h. In patients treated with t-PA, the results of the cited clinical and experimental studies indicate that adequate anticoagulation with intravenous heparin is essential during the first 24 h after administration of t-PA if procoagulant activity is to be inhibited- and maximal rates of coronary patency are to be achieved. It has been

argued that conjunctive anticoagulation with heparin may be less important when patients are given streptokinase, because the extensive fibrinogen degradation induced may have sufficient anticoagulant effects to prevent recurrent thrombosis, but the results of the SCATI and GISSI2/ International Study Group trials suggest that survival is improved in patients treated with conjunctive high-dose subcutaneous heparin[49]. Whether early administration of intravenous heparin would be of additional benefit in patients treated with streptokinase has not been defined by prospective studies. However, the extent and duration of anticoagulant effects induced by streptokinase may be variable; therefore, it is reasonable to administer heparin intravenously as opposed to subcutaneously during the first 24 h in patients treated with streptokinase to ensure that therapeutic levels of anticoagulant activity are achieved and maintained.

The timing and duration of heparin administration have also been poorly defined by clinical studies, and thus are the subject of controversy. In the Third Thrombolysis and Angioplasty in Myocardial Infarction study (TAMI-III), patients treated with t-PA (alteplase) were randomly assigned to receive either an intravenous bolus of 10,000 units of heparin or no initial heparin. Angiography was performed to determine coronary artery patency, and all patients were then treated with a continuous infusion of intravenous heparin for at least 24 h. Coronary artery patency was documented on the initial angiogram (approximately 60 min after initiation of treatment) in 79% of the patients given t-PA and heparin, compared with 73% treated with t-PA alone, and was 79% in both groups on the 9O-min angiogram . Although these data suggest that administration of heparin before t-PA does not increase the 9O-

min patency rate, they do not exclude more rapid recanalization in patients given conjunctive heparin, nor do they suggest that intravenous heparin is not necessary to ensure sustainedpatency.When these data are viewed in the 'context of more recent studies of the role of conjunctive heparin therapy in patients treated with t-PA, it appears that recurrent thrombosis after initial coronary artery recanalization is the most likely mechanism for the lower patency rates after 18 h documented in patients treated with t-PA without conjunctive heparin.

Recent results of a trial reported by the National Heart Foundation of Australia Coronary Thrombolysis Group suggest that continuation of intravenous heparin for more than 24 h after treatment with t-PA (alteplase) may not improve coronary patency rates at 7 to 10 days. In this trial, patients treated with t-PA were randomly assigned after 24 h of intravenous heparin administration to receive either intravenous heparin for 7 to 10 days (n = 99) or aspirin, 300 mg/d, plus dipyridamole, 300 mgld (n= 103)[50]. Coronary artery patency at 7 to 10 days was 81% in the heparin-treated group and 80% in those treated with the antiplatelet regimen . There also were no significant differences in the extent of coronary artery narrowing between the groups. Thus, prolonged administration of heparin does not appear to improve long-term coronary artery patency in patients treated with t-PA.

RECOMMENDATIONS

The available data suggest that increased procoagulant activity in patients treated with fibrinolytic agents is an important determinant of recurrent thrombosis. Results of clinical trials indicate that mortality is lower in patients treated with coronary thrombolysis when conjunctive heparin therapy is given. These data strongly support a role for heparin therapy in conjunction with coronary thrombolysis, a recommendation consistent with the guidelines recently published by the American College of Cardiology and the American Heart Association Task Force. In patients treated with t-PA, the results of recent clinical trials indicate that heparin should be given intravenously; initiated with a bolus of 5,000 units either before or within 90 min of initiation of the t-PA infusion, followed by an infusion of 1,000 units lh titrated to maintain the aPTT at 1.5 to 2 times control [51] . To avoid the tendency to underanticoagulate patients who are being treated with intravenous heparin, a standardized dosing regimen has been developed . In patients with deep venous thrombosis, use of this dosing protocol increased the percentage of patients in whom the aPTT was in the therapeutic range after 24 h compared with a historical control group. Conjunctive heparin should becontinued for at least 3 to 4 days, although treatment for 24 h may be sufficient in patients thought to be at a higher risk for bleeding. Although subcutaneous highdose heparin has been shown to decrease mortality in patients treated with streptokinase, the possibility that intravenous administration of heparin would be of greater benefit has not been addressed. Because intravenous administration of heparin is more likely to provide therapeutic levels of anticoagulant activity in the first 24 h, compared with subcutaneous administration

of the drug, and because there is no reason to suspect that the factors that promote recurrent thrombosis differ in patients treated with streptokinase, heparin should be given intravenously to these patients as well.

RESULTS

486 patients were thrombolysed during the time period July 2016 to June 2017. Analysis could be done on 54 patients based on our inclusion criteria.

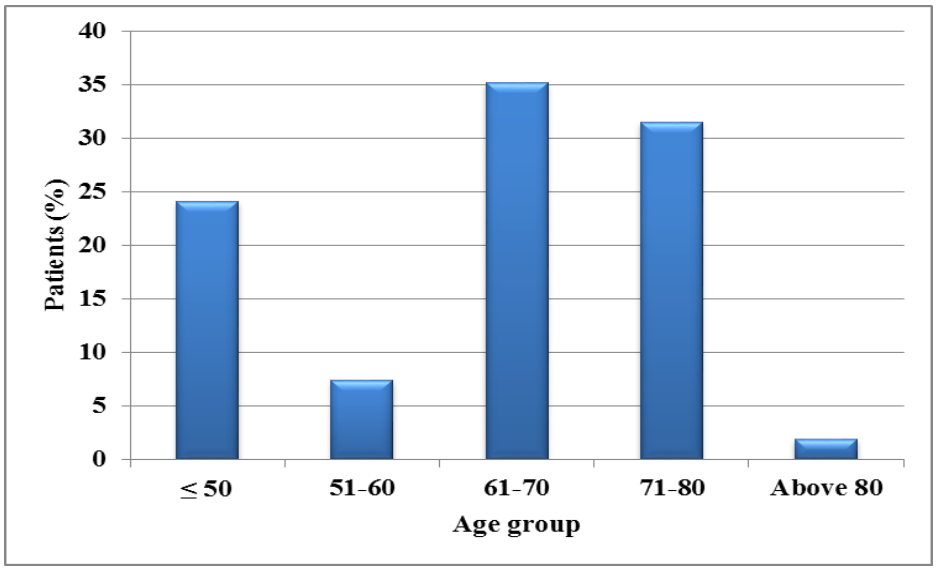
Mean age ranges between 39 to 87 with mean age 63.69 and standard deviation 11.86.

Table 1

Age wise Classification

Age group	Frequency	Percent
≤ 50	13	24.1
51-60	4	7.4
61-70	19	35.2
71-80	17	31.5
Above 80	1	1.9
Total	54	100.0

Figure 1



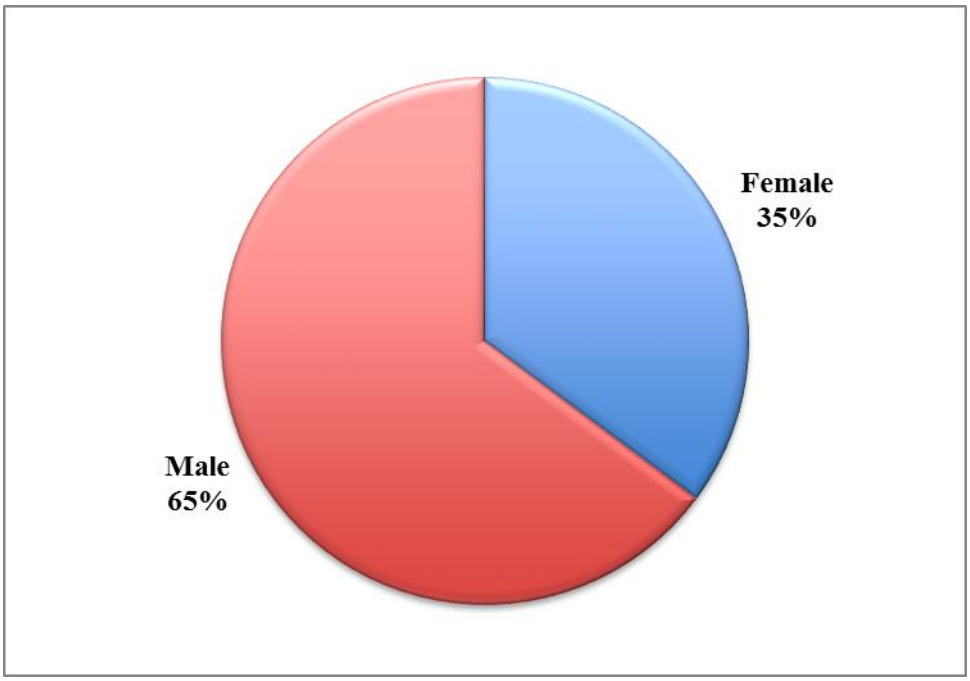
Age wise classification of patients

Table 2

Gender wise Classification

Gender	Frequency	Percent
Female	19	35.2
Male	35	64.8
Total	54	100.0

Figure 2



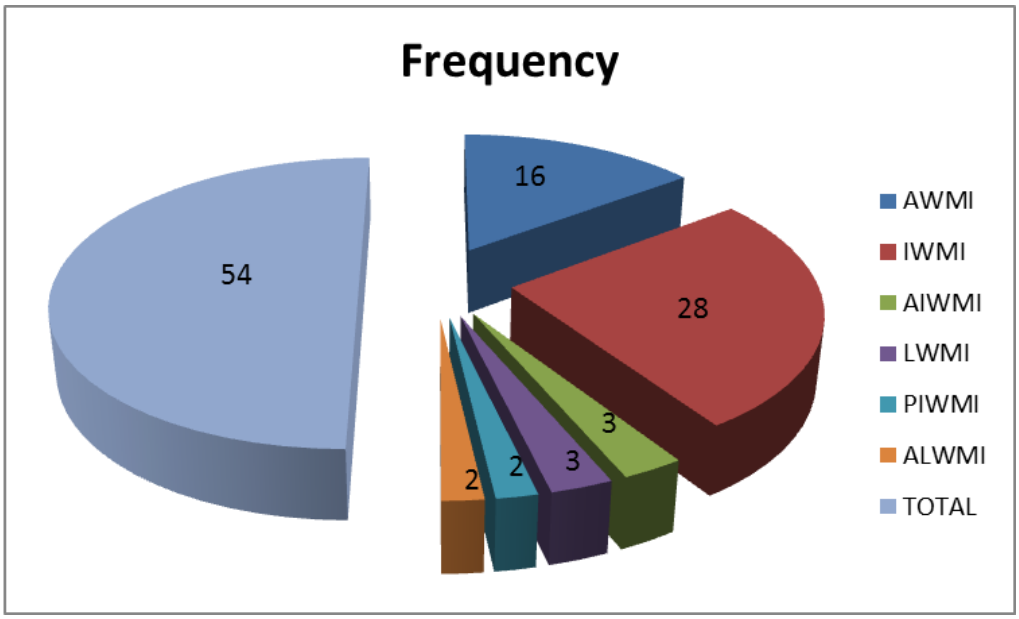
Gender wise classification

Table 3

Classification based on myocardial wall involvement

ECG	Frequency	Percent
AWMI	16	29.63%
IWMI	28	51.85%
AIWMI	3	5.56%
LWMI	3	5.56%
PIWMI	2	3.70%
ALWMI	2	3.70%
TOTAL	**54**	**100.00%**

Figure 3



Myocardial wall involvement

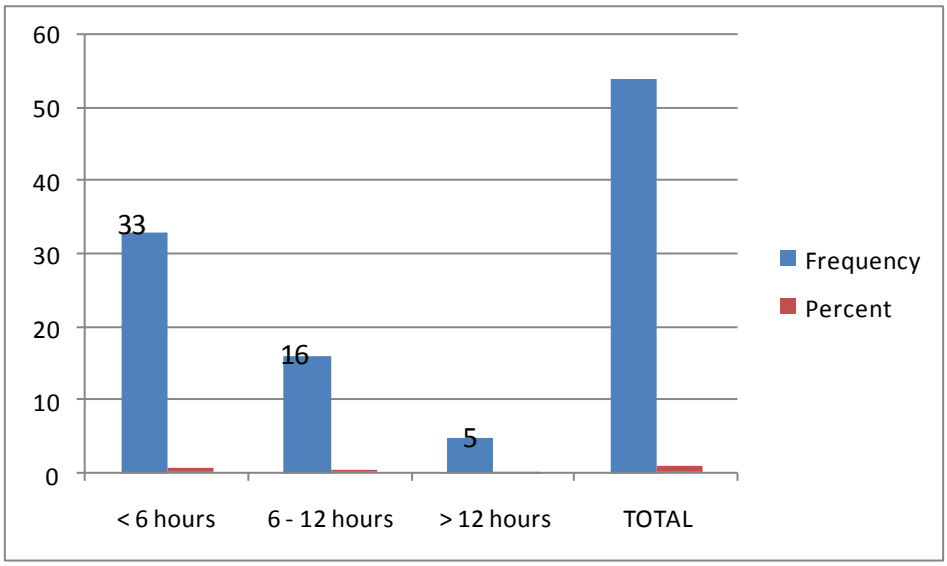
The time of thrombolysis after onset of pain was as follows. 33 patients (61.11%) presented within 6 hours of symptom onset. 16 patients within 6 - 12 hours of symptom onset. And 5 patients presented after 12 hours of symptom onset.

Table 4

Classification based symptom onset to thrombolysis time

Index pain to thrombolysis interval	Frequency	Percent
< 6hours	33	61.11%
6 - 12 hours	16	29.63%
> 12 hours	5	9.26%
TOTAL	**54**	**100.00%**

Figure 4



symptom onset to thrombolysis time

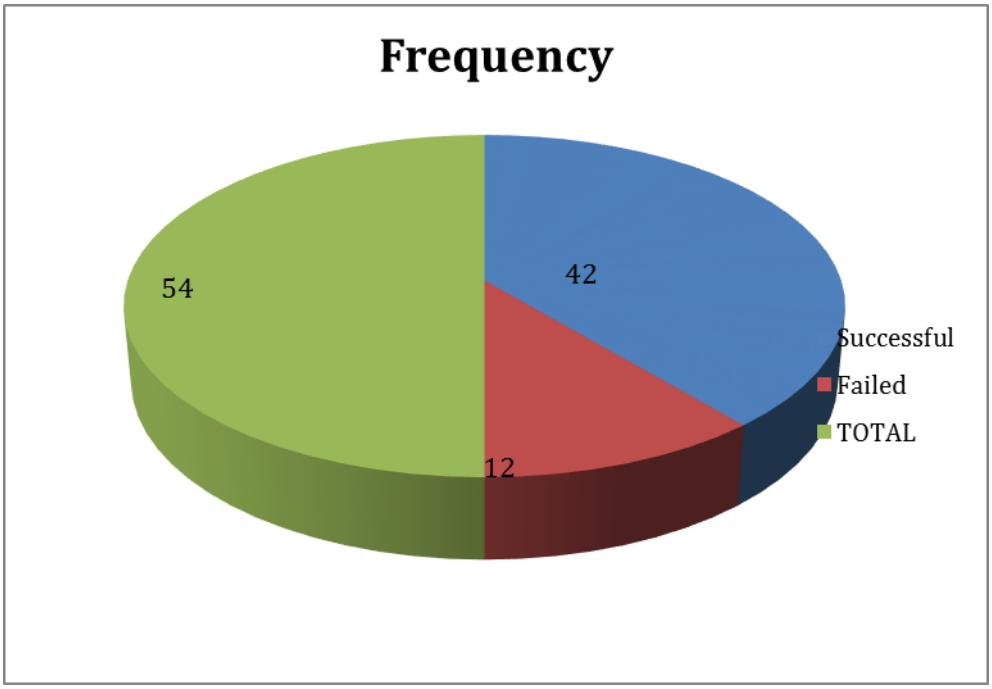
Out of 54 patients thrombolysed, 42 patients(77.78%) had successful thrombolysis and 12 patients(22.22%) had failed thrombolysis.

Table 5

Classification based on Thrombolysis outcome

Thrombolysis result	Frequency	Percent
Successful	42	77.78%
Failed	12	22.22%
TOTAL	**54**	**100.00%**

Figure 5



Thrombolysis outcome

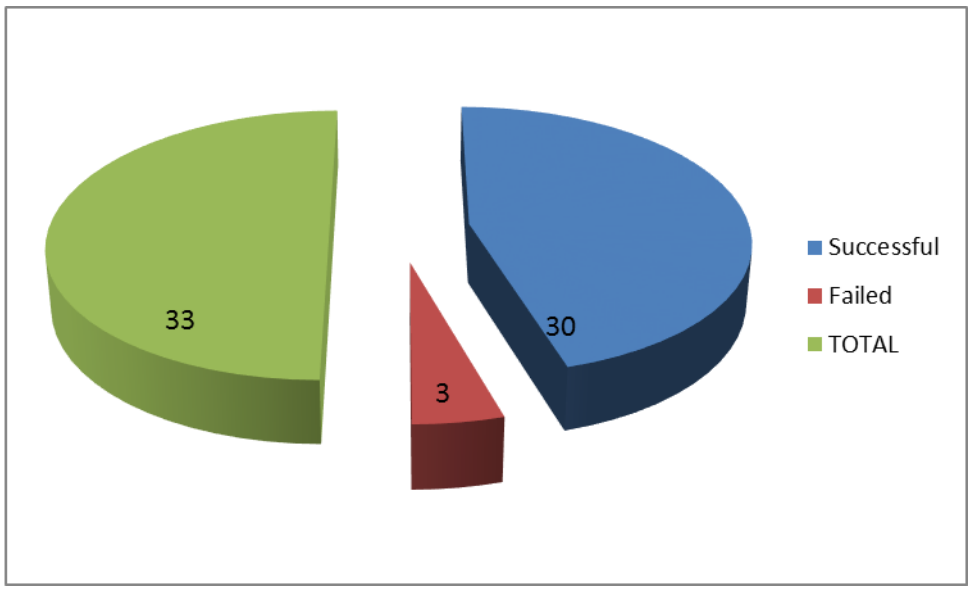
Successful thrombolysis based on time of presentation – 33 patients presented within 6 hours of symptom onset of which 30 patients(90.91%) had successful thrombolysis, and 3 patients(9.09%) had failed thrombolysis.

Table 6

Index pain to thrombolysis time < 6 hours and thrombolysis outcome

Thrombolysis result	Frequency	Percent
Successful	30	90.91%
Failed	3	9.09%
TOTAL	**33**	**100.00%**

Figure 6



Index pain to thrombolysis Interval < 6 hours frequency

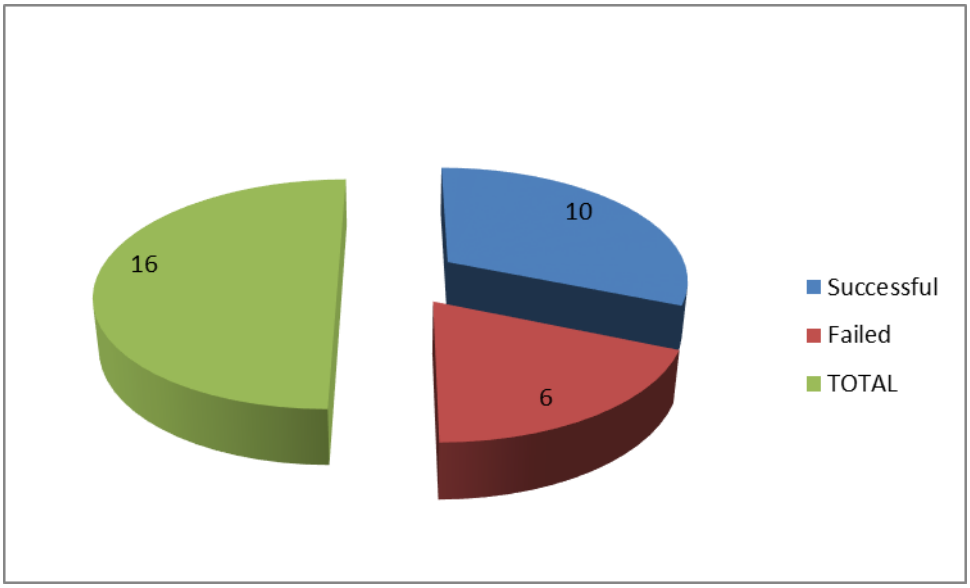
16 patients presented within 6 – 12 hours of symptom onset of which 10 patients(62.50%) had successful thrombolysis , and 6 patients(37.50%) had failed thrombolysis.

Table 7

Index pain to thrombolysis interval 6 - 12 hours and thrombolysis outcome

Thrombolysis result	**Frequency**	**Percent**
Successful	10	62.50%
Failed	6	37.50%
Total	**16**	**100.00%**

Figure 7



Index pain to thrombolysis interval 6 - 12 hours and thrombolysis outcome

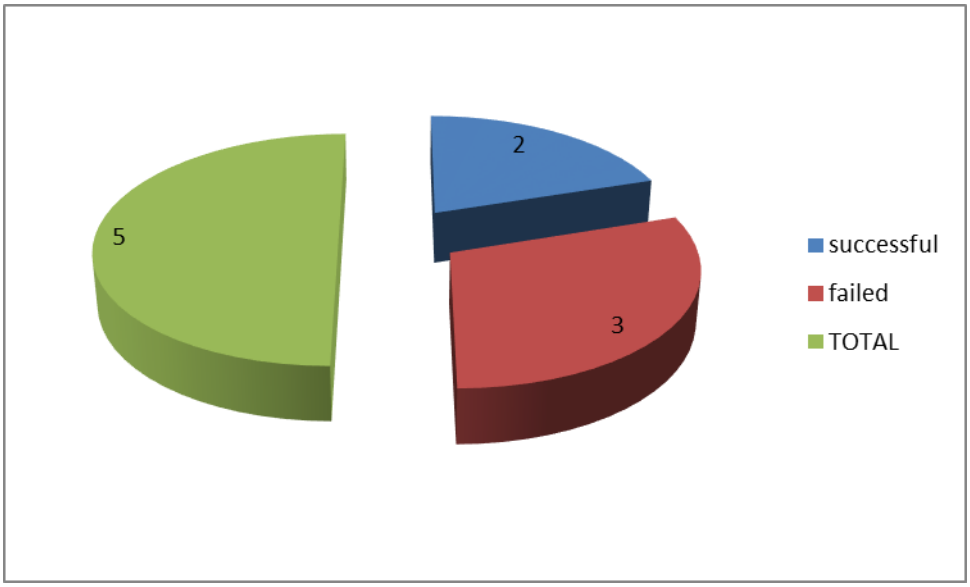
5 patients were thrombolysed after 12 hours of symptom onset of which 2 patients (40%) had successful thrombolysis, and 3 patients(60%) had failed thrombolysis.

Table 8

Index pain to thrombolysis time >12 hours and thrombolysis outcome

Thrombolysis result	**Frequency**	**Percent**
successful	2	40.00%
failed	3	60.00%
TOTAL	**5**	**100.00%**

Figure 8



Index pain to thrombolysis time >12 hours and thrombolysis outcome

50 – 70 seconds is the ideal APTT to maintain and to prevent reoclussion. As streptokinase was available in our hospital we wanted to know how many patients were in the therapeutic range of APTT after administration of streptokinase.

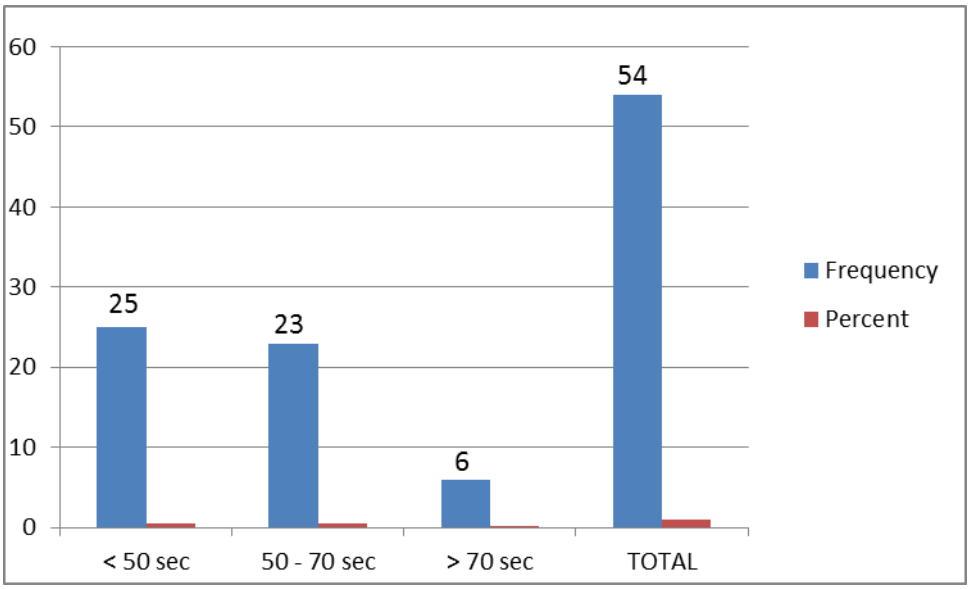
23 patients (42.59%) had APTT in the desired level of 50-70 seconds at the end of 3 hours of thrombolysis. 25 patients (46.30%) had APTT below the desired level. 6 patients(11.11%) had APTT above the desired level.

Table 9

Classification of patients based on APTT level at 3 hours

APTT at 3hrs	Frequency	Percent
< 50 sec	25	46.30%
50 - 70 sec	23	42.59%
> 70 sec	6	11.11%
TOTAL	**54**	**100.00%**

Figure 9



Classification of patients based on APTT level at 3 hours

APTT at 6 hours after thrombolysis

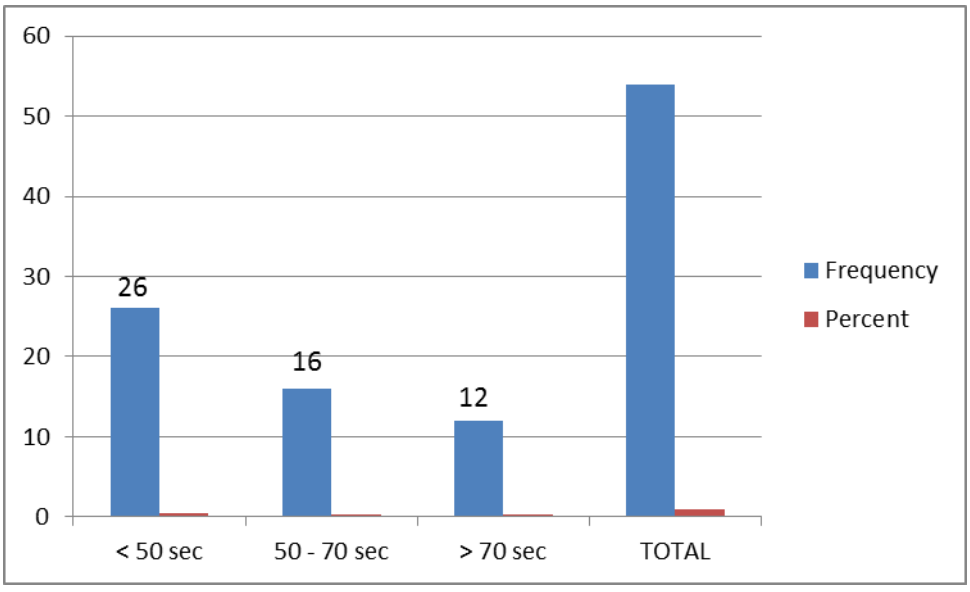
16 patients(29.63%) had APTT within the desired therapeutic level at the end of 6 hours after thrombolysis.

Table 10

Classification of APTT at the end of 6 hours

APTT at 6 hrs	Frequency	Percent
< 50 sec	26	48.15%
50 - 70 sec	16	29.63%
> 70 sec	12	22.22%
Total	**54**	**100.00%**

Figure 10



Classification of APTT at the end of 6 hours

APTT at the end of 9 hours

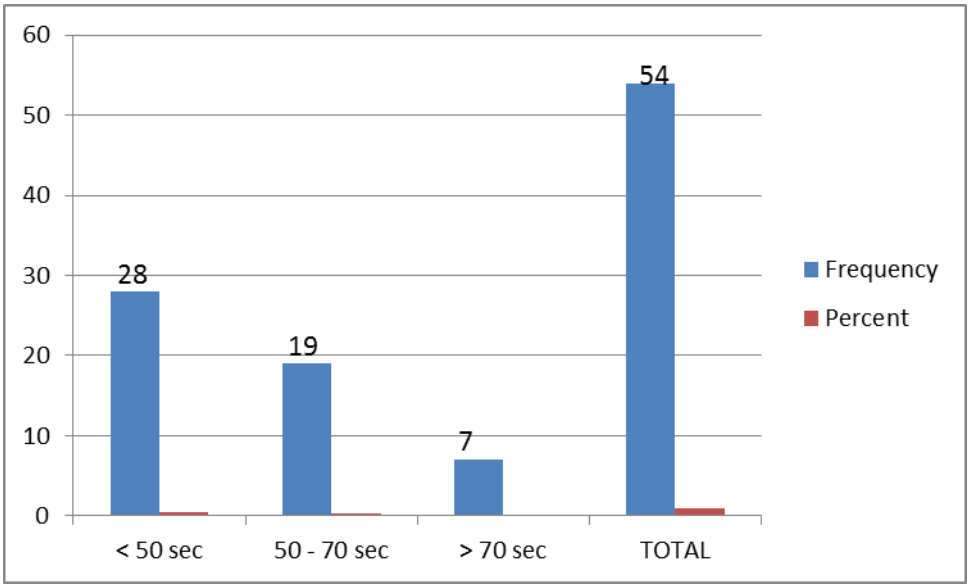
19 patients were in the desired APTT value of 50 – 70 seconds.

Table 11

Classification of patients based on APTT values at 9 hours

APTT at 9 hrs	Frequency	Percent
< 50 sec	28	51.85%
50 - 70 sec	19	35.19%
> 70 sec	7	12.96%
Total	**54**	**100.00%**

Figure 11



Classification of APTT at the end of 9 hours

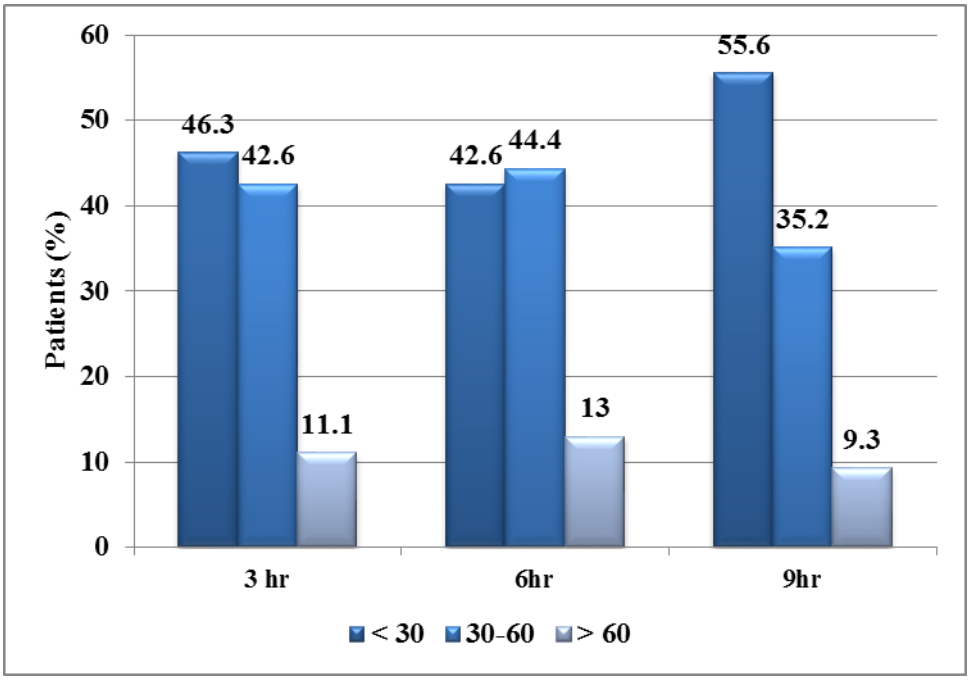
23 patients had PT below 30 seconds, 24 patients had between 30-60 seconds and 7 patients had >60 seconds.

Table 12

Classification of patients based on PT at 3,6 and 9 hours

PT	3hr		6hr		9hr	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
< 30	25	46.3	23	42.6	30	55.6
30-60	23	42.6	24	44.4	19	35.2
> 60	6	11.1	7	13.0	5	9.3
Total	54	100	54	100	54	100

Figure 12



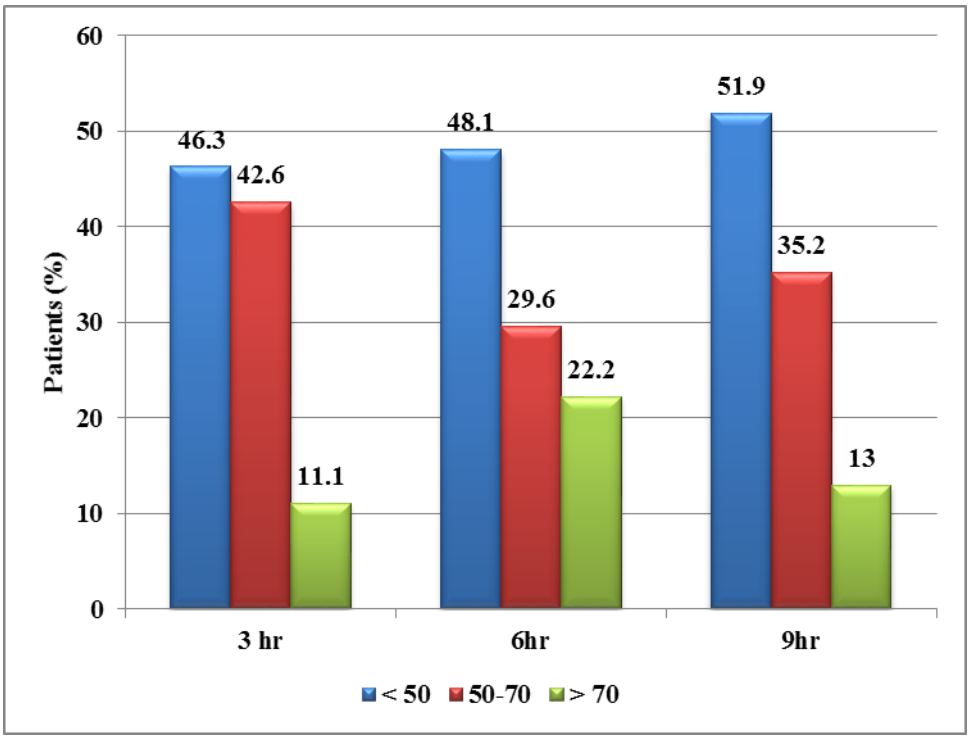
Classification of patients based on PT at 3,6 and 9 hours

Table 13

Classification of patients based on APTT at 3, 6 and 9 hours

APTT	3hr		6hr		9hr	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
< 50	25	46.3	26	48.1	28	51.9
50-70	23	42.6	16	29.6	19	35.2
> 70	6	11.1	12	22.2	7	13.0
Total	54	100	54	100	54	100

Figure 13



Classification of patients based on APTT at 3, 6 and 9 hours

Comparison between APTT values of patients consuming alcohol and who do not consume alcohol.17 patients were consuming alcohol and 37 patients were not consuming alcohol.

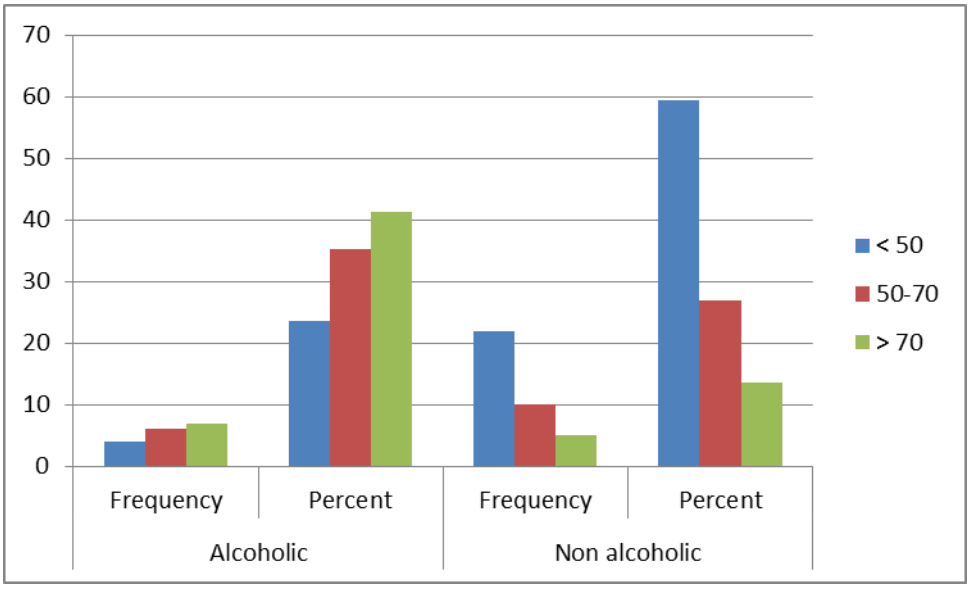
P = 0.025.

Table 14

Comparison of alcohol habit and APTT values

APTT	Alcoholic		Non alcoholic	
	Frequency	Percent	Frequency	Percent
< 50	4	23.5	22	59.5
50-70	6	35.3	10	27.0
> 70	7	41.2	5	13.5

Figure 14



Comparison of alcohol habit and APTT values

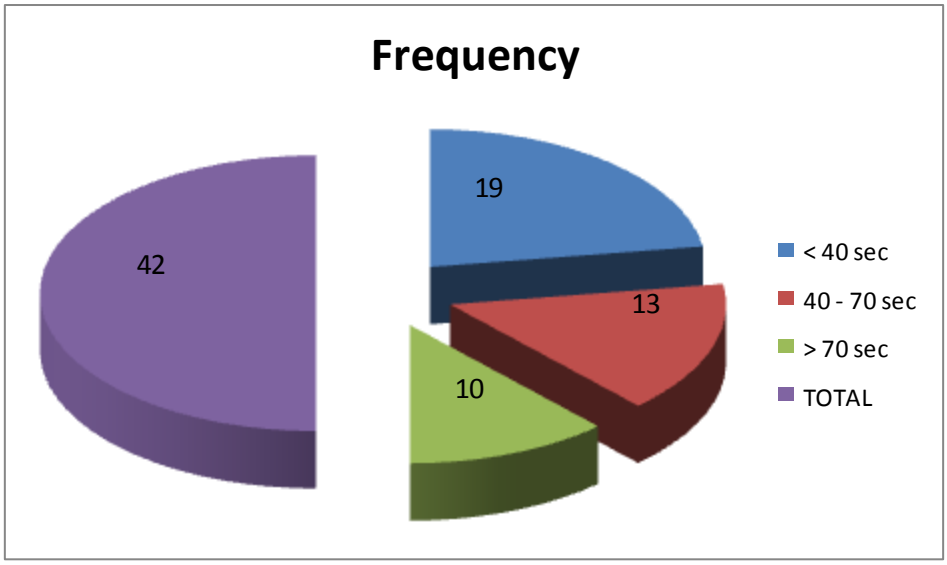
Relationship between successful thrombolysis and APTT value at 6 hours Out of 42 successful thrombolysis patients , 19 patients (45.24%) had APTT values below the therapeutic range , 13 patients (30.95%) were in the therapeutic range , and 10 patients (23.81%) were in the supratherapeutic range.

Table 15

APTT values and success of thrombolysis

APTT at 6 hrs	**Frequency**	**Percent**
< 50 sec	19	45.24%
50 - 70 sec	13	30.95%
> 70 sec	10	23.81%
TOTAL	**42**	**100.00%**

Figure 15



APTT values and success of thrombolysis

Relationship between failed thrombolysis and APTT

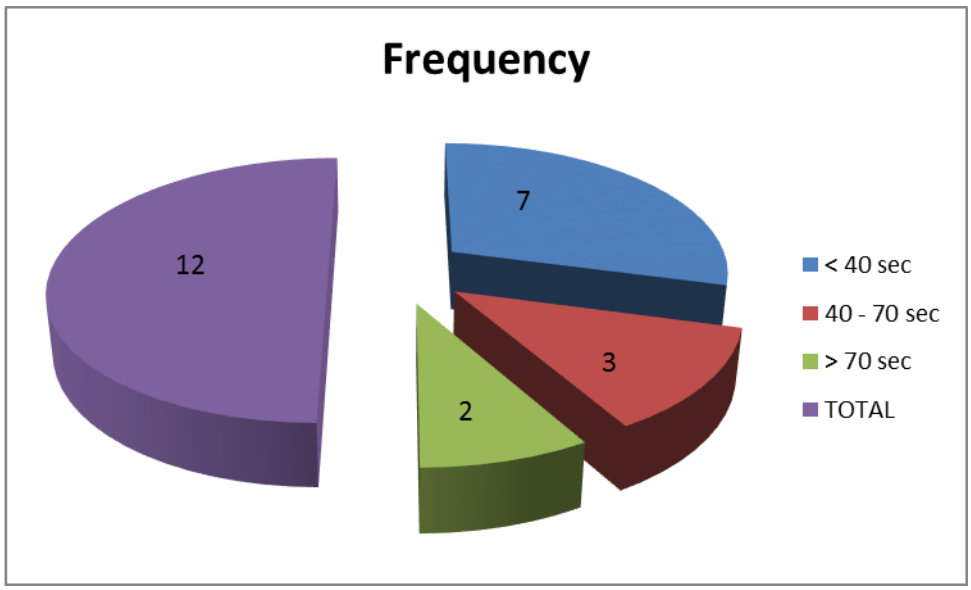
12 patients had failed thrombolysis , out of which 7 patients (58.33%) were in the sub therapeutic range, 3 patients (25%) were in the therapeutic range and 2 patients (16.67%) were in the supra therapeutic range.

Table 16

Failed thrombolysis and APTT at 6 hours

APTT at 6 hrs	**Frequency**	**Percent**
< 50 sec	7	58.33%
50 - 70 sec	3	25.00%
> 70 sec	2	16.67%
TOTAL	**12**	**100.00%**

Figure 16



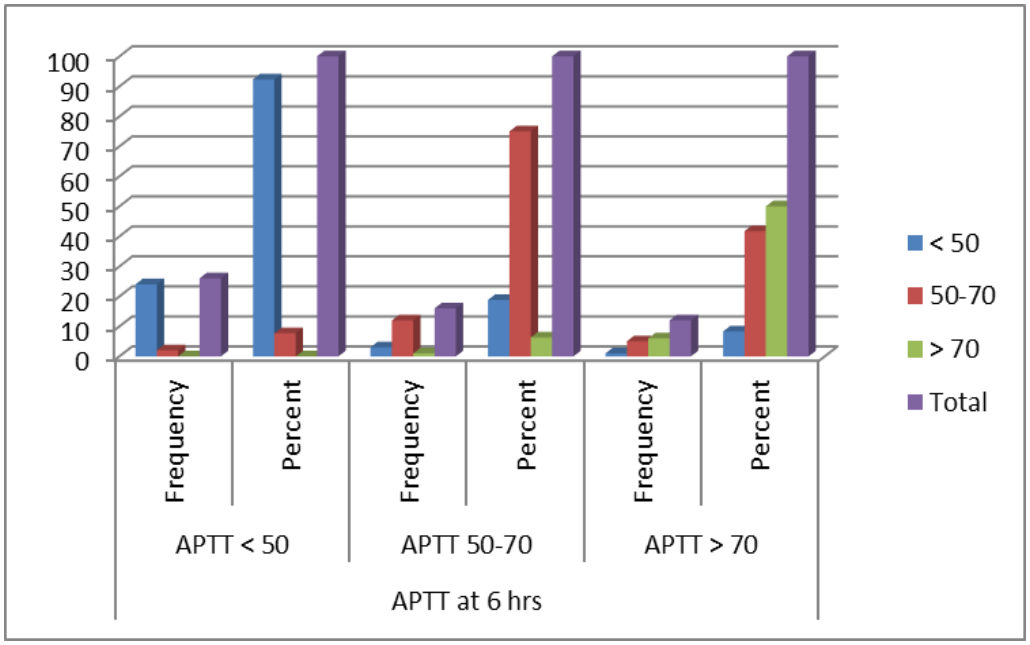
Failed thrombolysis and APTT at 6 hours

Table 17

Comparison of patients with APTT at 6 hours and APTT at 9 hours

APTT at 9 hrs	APTT at 6 hrs					
	APTT < 50		APTT 50-70		APTT > 70	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
< 50	24	92.3	3	18.8	1	8.3
50-70	2	7.7	12	75.0	5	41.7
> 70	0	0	1	6.3	6	50.0
Total	26	100	16	100	12	100

Figure 17



Comparison of patients with APTT at 6 hours and APTT at 9 hours

$\chi^2 = 45.533$ $P < 0.001$.

Kappa score for the agreement between APTT at 6 hours and 9hours is 0.640.

DISCUSSION

DISCUSSION

Most patients were in the age group of 61 – 70 years. Of the 54 patients 19 were females and 35 were males, male female ratio was 1.8:1.

51.85% patients had isolated inferior wall involvement based on ecg criteria , < 30% patients had involvement of anterior wall, rest of them had overlapping involvement.

61% patients were thrombolysed within 6 hours of symptom onset, 9.26% patients were thrombolysed after 12 hours of symptom onset.

42(77.78%) patients had successful thrombolysis and 12(22.22%) patients had failed thrombolysis. A study by L Bhatia et al found ST segment resolution in 53% of patients.

90% patients had successful thrombolysis when thrombolysis was initated within 6 hours of symptom onset.

60% patients had failed thrombolysis when they were thrombolysed after 12 hours of symptom onset. So early thrombolysis has more chances of a successful thrombolysis.

In our study only 29.63% patients had APTT in the therapeutic level of 50 – 70 seconds which was similar to study by Arnout J et al where 32% patients were in the therapeutic range. No association was found between alcohol use and APTT values. 17(31.48%) patients were using alcohol in our study.

There was a significant relation between APTT at the end of 6 hours and APTT at the end of 9 hours and may be due to heparinisation at the end of 6 hours.

Based on the above data 48.15% patients had their APTT in the sub therapeutic level at the end of 6 hours after thrombolysis. These patients may have been benefited if they were heparinised at an earlier time. This needs further study by comparing two groups based on early heparinisation before 6 hours and at 6 hours (standard heparinisation), and comparing the outcome in these two group based on resolution of ECG , decrease in pain and angiographic findings.

CONCLUSION

CONCLUSION

1. Early heparinisation may be considered in those patients who have non resolving ST segment 90 minutes after thrombolysis , or those patients who have continuing pain even after thrombolysis.

2. A significant correlation was found between APTT at 6hours and APTT at 9 hours that is patients who were in the therapeutic range at the end of 6 hours were also maintained at the end of 9 hours probably due to heparinisation at the end of 6 hours after thrombolysis.

3. There is suboptimal anticoagulation in MI.

LIMITATIONS

LIMITATIONS OF STUDY

1. Sample size was small.

2. Because analysis could be performed on patients who survived long enough. So this data is less representative of patients at high risk for early death.

3. The lack of standardized or normalized methods for APTT determination and also because of the variation in responsiveness of the APTT to heparin among different reagents.

RECOMMENDTIONS

Half of the patients APTT values were below the therapeutic level after thrombolysis, so early heparinisation could be beneficial for these patients. Further studies are needed to compare patients between two groups with one group subjected to early heparinisation and other group to routine heparinisation at 6 hours and comparing the outcome between the two groups.

ANNEXURES

MASTER CHART

Key to master chart:

Chest pain: 1-present
2-absent

Breathlessness: 1-present
2-absent

CAD: 1-present
2-absent

Stroke: 1-present
2-absent

Systemic htn: 1-present
2-absent

Type 2 DM: 1-present
2-absent

Dyslipidemia: 1-present
2-absent

Smoker: 1-yes
2-no

Alcohol use: 1-yes
2-no

On anti htn drugs: 1-yes
2-no

OHA: 1-yes
2-no

Insulin use: 1-yes
2-no

Antiplatelets: 1-yes
2-no

Killip class: 1-class 1
2-class 2
3-class 3
4-class 4

Hemoglobin: 1-<8 mg/dl
2-8-12 mg/dl
3->12 mg/dl

PT: 1-<30 sec
2-30-60 sec
3->60 sec

APTT: 1-<50 sec
2-50-70 sec
3->70 sec

ECG: 1-AWMI
2-IWMI
3-AWMI+IWMI
4-LWMI
5-Posterior+IWMI
6-AWMI+LWMI

Index pain to thrombolysis time: 1-<6 hrs
2- 6-12 hrs
3->12 hrs

Thrombolysis result: 1-successful
2-failed

SERIAL NUMBER	1	2	3	4	5	6	7	8	9	10	11
NAME	BALAN	VEDAHAVATHY	MALINI	KESHAVAM	SISILY	MURALI	NEELI	RADHA	VELAYUDHAM	MANIKKAM	MALLIK
AGE	75	87	75	75	75	72	73	78	75	65	70
SEX	M	F	F	M	F	M	F	F	M	M	M
CHEST PAIN	1	1	1	1	1	1	1	1	2	2	2
BREATHLESSNESS	1	2	2	2	1	2	2	2	2	2	2
CAD	1	1	2	2	2	2	2	2	1	2	2
STROKE	2	2	2	2	2	2	2	2	2	2	2
SYSTEMIC HYPERTENSION	1	1	1	2	2	2	2	1	1	2	2
TYPE 2 DM	2	2	2	2	1	2	1	1	1	2	2
DYSLIPIDEMIA	2	2	2	2	2	2	2	2	2	2	2
SMOKER	1	1	2	1	2	1	2	2	2	2	1
ALCOHOLIC	1	1	2	2	2	2	2	2	2	2	2
ANTIHYPERTENSIVES	2	2	2	2	2	2	2	1	1	2	2
OHA	2	2	2	2	1	2	1	2	1	2	2
INSULIN	2	2	2	2	2	2	2	2	2	2	2
ANTIPLATELETS	2	2	2	2	2	2	2	2	1	2	2
KILIP CLASS	2	1	1	1	1	1	1	4	1	1	2
HB	3	3	3	3	3	3	3	3	2	3	3
PT AT 3 HRS	2	2	1	3	2	1	1	2	1	1	2
PT AT 6 HRS	2	2	1	3	2	1	1	2	1	1	2
PT AT 9 HRS	2	2	1	3	2	1	1	2	1	1	2
APTT AT 3HRS	2	2	1	2	2	1	1	2	1	2	2
APTT AT 6HRS	2	2	1	2	1	1	1	2	1	1	2
APTT AT 9 HRS	2	2	1	2	1	1	1	2	1	1	2
ECG	1	2	2	1	2	2	1	2	1	1	1
TINTERVAL	1	1	1	1	2	1	2	2	2	1	2
THROMBOLYSIS RESULT	1	1	1	1	2	1	1	2	1	1	1

22	21	20	19	18	17	16	15	14	13	12	SERIAL NUMBER
SAROJA	MARIKANNU	RANI	SHANKARAN	RAJAN	MEERA	PONNI	MARIYAN	AYISHA	KALYANI	MARUTHAMUTHU	NAME
51	48	49	48	48	63	70	77	65	72	62	AGE
F	M	F	M	M	F	F	M	F	F	M	SEX
1	1	1	1	1	1	2	1	1	1	1	CHEST PAIN
2	2	2	2	2	2	1	2	2	2	2	BREATHLESSNESS
2	2	2	2	2	2	2	2	2	2	2	CAD
2	2	2	2	2	2	2	2	2	2	2	STROKE
2	2	1	2	2	2	2	2	2	2	2	SYSTEMIC HYPERTENSION
2	2	2	2	2	2	1	2	2	2	2	TYPE 2 DM
2	2	2	2	2	2	2	2	2	2	2	DYSLIPIDEMIA
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2	1	2	1	1	2	2	2	2	2	1	ALCOHOLIC
2	2	1	2	2	2	2	2	2	2	2	ANTIHYPERTENSIVES
2	2	2	2	2	2	1	2	2	2	2	OHA
2	2	2	2	2	2	2	2	2	2	2	INSULIN
2	2	2	2	2	2	2	2	2	2	2	ANTIPLATELETS
1	1	1	1	1	1	3	1	1	1	1	KILIP CLASS
3	3	3	3	3	1	3	3	3	3	3	HB
2	1	1	1	2	1	2	1	1	1	1	PT AT 3 HRS
2	1	1	1	2	1	1	1	1	1	1	PT AT 6 HRS
2	1	1	1	2	1	1	1	1	1	1	PT AT 9 HRS
1	1	1	1	2	1	1	1	1	1	1	APTT AT 3HRS
1	1	1	1	2	1	1	2	1	1	1	APTT AT 6HRS
1	1	1	1	2	1	1	1	1	1	1	APTT AT 9 HRS
2	2	2	2	2	1	1	4	5	2	2	ECG
1	1	1	1	2	1	2	1	1	3	1	TINTERVAL
1	1	1	1	1	1	1	1	1	1	1	THROMBOLYSIS RESULT

33	32	31	30	29	28	27	26	25	24	23	SERIAL NUMBER
ARIVUDINANBI	ANNA	MADHAVAN	KURAVAN	CHINNASAMI	BALAN	AANDI	THANKAMANI	GOPALAN	DEVAKY	SURESH	NAME
76	64	48	50	45	68	66	73	73	65	49	AGE
M	F	M	M	M	M	M	F	M	F	M	SEX
1	1	1	1	1	1	1	1	1	1	1	CHEST PAIN
2	2	2	2	2	2	2	2	2	2	1	BREATHLESSNESS
2	2	1	2	1	2	2	2	2	2	2	CAD
2	2	2	2	2	2	2	2	2	2	2	STROKE
1	1	2	2	2	1	2	2	1	2	2	SYSTEMIC HYPERTENSION
1	1	2	2	2	2	2	2	1	2	2	TYPE 2 DM
2	2	2	2	2	2	2	2	2	2	2	DYSLIPIDEMIA
2	2	1	1	1	1	1	2	2	2	1	SMOKER
2	2	1	1	1	2	1	2	2	2	2	ALCOHOLIC
2	1	2	2	2	2	2	2	1	2	2	ANTIHYPERTENSIVES
2	1	2	2	2	2	2	2	1	2	2	OHA
2	2	2	2	2	2	2	2	2	2	2	INSULIN
2	1	2	2	2	2	2	2	2	2	2	ANTIPLATELETS
2	1	1	1	1	1	2	1	3	2	1	KILIP CLASS
1	3	3	3	3	3	3	3	3	3	3	HB
1	2	2	1	2	2	3	1	1	1	1	PT AT 3 HRS
1	2	2	2	2	3	3	1	1	1	1	PT AT 6 HRS
1	2	2	2	1	2	2	1	1	1	1	PT AT 9 HRS
2	1	2	1	2	2	3	2	1	1	1	APTT AT 3HRS
1	2	1	2	3	3	3	1	1	1	1	APTT AT 6HRS
1	2	2	2	2	3	3	1	1	1	1	APTT AT 9 HRS
2	2	5	2	2	2	6	2	1	6	1	ECG
1	1	1	1	1	1	3	2	3	1	2	TINTERVAL
2	1	1	1	1	1	1	2	2	1	2	THROMBOLYSIS RESULT

44	43	42	41	40	39	38	37	36	35	34	SERIAL NUMBER
RAJAN	GOURI	RUDRAN	EDLHOSE	ANDAVAN	RAMAN	SUPPAMANI	ILAKKYA	PAPPA	CHELLAM	AZHAGAR	NAME
66	55	70	43	70	58	74	63	75	70	73	AGE
M	F	M	M	M	M	M	F	F	F	M	SEX
1	1	1	1	1	1	1	1	1	1	1	CHEST PAIN
2	2	2	2	2	2	2	2	2	2	2	BREATHLESSNESS
2	2	2	2	2	2	2	2	2	2	2	CAD
2	2	2	2	2	2	2	2	2	2	2	STROKE
2	1	2	2	2	2	2	1	2	2	2	SYSTEMIC HYPERTENSION
2	2	2	2	2	2	2	1	2	2	2	TYPE 2 DM
2	2	2	2	2	2	2	2	2	2	2	DYSLIPIDEMIA
1	2	1	1	2	1	1	2	2	2	1	SMOKER
1	2	2	2	2	1	1	2	2	2	2	ALCOHOLIC
2	1	2	2	2	2	2	1	2	2	2	ANTIHYPERTENSIVES
2	2	2	2	2	2	2	1	2	2	2	OHA
2	2	2	2	2	2	2	1	2	2	2	INSULIN
2	2	2	2	2	2	2	2	2	2	2	ANTIPLATELETS
1	1	1	1	1	1	1	3	3	1	1	KILIP CLASS
3	3	3	3	3	3	3	2	3	3	3	HB
2	3	2	1	2	2	2	1	3	2	2	PT AT 3 HRS
1	3	2	1	2	2	1	1	3	2	2	PT AT 6 HRS
1	3	1	1	1	2	1	1	3	1	2	PT AT 9 HRS
3	3	1	1	2	3	2	1	2	2	1	APTT AT 3HRS
3	3	1	2	1	3	3	1	2	2	2	APTT AT 6HRS
2	3	1	2	1	3	1	1	2	3	1	APTT AT 9 HRS
2	2	2	2	2	4	3	1	1	2	2	ECG
2	1	1	1	1	2	2	3	1	1	1	TINTERVAL
1	1	1	1	1	1	1	2	1	2	2	THROMBOLYSIS RESULT

54	53	52	51	50	49	48	47	46	45	SERIAL NUMBER
ANANDHAN	GOPI	KUNJAMMA	RAVI	SAIDHALI	JONSON	ELANKO	KUNJAPPAN	MADHAVAN	RAYAN	NAME
39	54	80	50	65	40	70	61	45	68	AGE
M	M	F	M	M	M	M	M	M	M	SEX
1	1	1	1	1	1	1	1	1	2	CHEST PAIN
2	2	1	2	1	2	2	2	2	2	BREATHLESSNESS
2	2	2	2	2	2	2	2	2	1	CAD
2	2	2	2	2	2	2	2	2	2	STROKE
1	1	2	1	2	2	2	2	2	1	SYSTEMIC HYPERTENSION
2	1	2	2	2	2	2	2	2	2	TYPE 2 DM
2	2	2	2	2	2	2	2	2	2	DYSLIPIDEMIA
1	1	2	1	1	1	1	1	1	1	SMOKER
2	2	2	2	2	1	1	1	1	1	ALCOHOLIC
1	1	2	1	2	2	2	2	2	2	ANTIHYPERTENSIVES
2	1	2	2	2	2	2	2	2	2	OHA
2	2	2	2	2	2	2	2	2	2	INSULIN
2	2	2	2	2	2	2	2	2	2	ANTIPLATELETS
1	2	4	1	2	1	1	1	1	3	KILIP CLASS
3	3	3	3	3	1	3	3	3	3	HB
2	3	2	3	1	1	2	1	2	2	PT AT 3 HRS
2	3	2	2	2	2	2	2	2	3	PT AT 6 HRS
2	3	3	2	1	2	1	1	2	2	PT AT 9 HRS
2	3	2	3	1	2	2	1	2	2	APTT AT 3HRS
1	3	3	3	1	2	2	2	3	3	APTT AT 6HRS
2	2	2	3	1	1	2	2	2	3	APTT AT 9 HRS
1	3	1	4	1	2	2	2	2	3	ECG
1	1	2	1	2	1	1	2	1	3	TINTERVAL
1	1	1	1	2	1	2	1	2	2	THROMBOLYSIS RESULT

PATIENT CONSENT FORM

TITLE OF THE STUDY: A STUDY ON COAGULATION PROFILE OF PATIENTS THROMBOLYSED WITH STREPTO KINASE IN ACUTE ST ELEVATION MYOCARDIAL INFARCTION

Study Centre: Mahatma Gandhi Memorial Government Hospital, Trichy.

Patient's Name: **Age/Sex:**

Parent/Guardian's Name:

Address:

- The details of the study have been provided to me in writing and explained to me in my own language. I confirm that I have understood the above study and had the opportunity to ask questions about A STUDY ON COAGULATION PROFILE OF PATIENTS THROMBOLYSED WITH STREPTOKINASE IN ACUTE ST ELEVATION MYOCARDIAL INFARCTION.
- I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without affecting the medical care that will normally be provided by the hospital.
- I understand that the doctor involved in the study does not require my permission, to monitor and assess me for various medical parameters
- I agree not to restrict the use of any data or results that arise from this study, provided such a use is only for scientific purpose(s).
- I fully give consent to take part in the study and I have also been explained about the complications that may arise due to the surgical techniques
- I give my consent for the study involving treatment for PATIENTS THROMBOLYSED WITH STREPTOKINASE IN ACUTE ST

ELEVATION MYOCARDIAL INFARCTION and it was explained to me that this study methods does not alter any standard management for this diseases and is in no way will be affecting the patients health as mentioned in the patient information sheet.

- I consent wholeheartedly after understanding that the study is taken up for the benefit for me

Signature/Thumb impression of the patient

Date:

Place:

Signature of the investigator

சுய ஒப்புதல் படிவம்

தலைப்பு: அவசர மாரடைப்பில் ஸ்டெட்ரெப்டோகைனேசு மருந்து செலுத்துவதால் இரத்தத்தின் உரையும்தன்மையின் நிலை பற்றிய ஆய்வு

பங்கு பெறுபவர் பெயர்
பரிசோதனை செய்யும் இடம்
பரிசோதனை எண்
நோயாளி எண்

1. நான் இப்பரிசோதனையில் _____ தேதியிட்ட தகவல் படிவத்தினை படித்து புரிந்து கொண்டேன் என உறுதியளிக்கிறேன். அதில் உள்ள சந்தேகங்களை நிவர்த்தி செய்ய வாய்ப்பு அளிக்கப்பட்டேன்.
2. இந்த ஆய்வில் என்னுடைய பங்களிப்பு சுய விருப்பத்தின் பேரில் தான் என்பதையும், இந்த ஆய்வில் இருந்து எந்த நிலையிலும் காரணம் தெரிவிக்காமல் விலகிக் கொள்ளவும் எனக்கு உரிமை உள்ளதையும் அறிந்துகொண்டேன். மேலும் இந்த ஆய்வு என்னுடைய மருத்துவ சிகிச்சையை எந்த விதத்திலும் பாதிக்காது என உணர்ந்துகொண்டேன்.
3. என்னுடைய பரிசோதனை முடிவுகளை எப்பொழுது வேண்டுமானாலும் பயன்படுத்திக்கொள்ள இச்சோதனை அதிகாரிகளுக்கு முழு உரிமை அளிக்கிறேன்.
4. இதன் மூலம் நான் இச்சோதனையில் பங்குபெற முழு சம்மதம் அளிக்கிறேன்.

    1. நோயாளியின் கையொப்பம்
    2. பரிசோதகரின் கையொப்பம்
    3. உறவினர் கையொப்பம்

திருச்சி கி.ஆ.பெ. விசுவநாதம் மருத்துவக்கல்லூரி மற்றும் மகாத்மா காந்தி நினைவு மருத்துவமனையில் அறுவை சிகிச்சைக்காக அனுமதிக்கப்பட்டுள்ளேன். மருத்துவ அறுவை சிகிச்சை உயர்நிலை பயிற்சி படிப்பில் மூன்றாம் ஆண்டில் பயிலும் மருத்துவர் அவர்களின் ஆய்வினால் எனது உடலுக்கோ மருத்துவ முறையிலோ எந்தவித பாதிப்பும் ஏற்படாது என்பதை எடுத்துக் கூறினார். மருத்துவர் இந்த ஆய்வினை செய்து பதிவு செய்து கொள்ள என் சுய நினைவோடு முழு சம்மதம் தெரிவிக்கிறேன்.

இப்படிக்கு,

PATIENT INFORMATION SHEET

Name :

Age :

Sex :

Education :

Occupation :

Duration of Illness :

Informant :

Relationship with the patient :

I ---------- ---------- is willing to include my particulars about -------- ---------- in the study titled A STUDY ON COAGULATION PROFILE OF PATIENTS THROMBOLYSED WITH STREPTOKINASE IN ACUTE ST ELEVATION MYOCARDIAL INFARCTION.

SIGNATURE

நோயாளியின் தகவல் படிவம்

பெயர் :

வயது :

பாலினம் :

கல்வி :

தொழில் :

எத்தனை நாட்கள் தொந்தரவு :

தகவல் தந்த நபர் :

நோயாளியின் உறவினர் :

---------- ஆகிய நான் என்னுடைய நோய் பற்றிய தகவல்களை அவசர மாரடைப்பில் ஸ்டெட்ரெப்டோகைனேசு மருந்து செலுத்துவதால் இரத்தத்தின் உரையும்தன்மையின் நிலை பற்றி அறிந்து இச்சோதனையில் சேர்த்துக்கொள்ள சம்மதிக்கிறேன்.

PROFORMA

ACUTE MI : A CLINICAL PROFILE

BIODATA

Name | Age | DOA | Sex | Occupation

IPNo. | Home Phone | Cell Phone | Residence

SYMPTOMS AT TIME OF PRESENTATION

☐ Chest Pain > 20 min ☐ Sweating ☐ Pain Exertional ☐ Relieved by Rest ☐ Unexplained Fatigue

☐ Breathlessness ☐ Nausea

☐ Epigastric Pain

Chest Pain Duration in Hours

Radiation of Chest Pain

☐ Radiation to Right Arm ☐ Radiation to Left Shoulder ☐ Radiation to Jaw

☐ Radiation to Left Arm ☐ Radiation to Right Shoulder

PAST HISTORY

CAD ☐ Stroke ☐ Systemic Hypertension ☐ Diabetes Mellitus ☐ Dyslipidemia

PERSONAL HISTORY

Smoking (in pack years) | Alcohol Intake (in drinks/day)

Drug History

Antihypertensives

☐ Beta Blockers ☐ CCBs

☐ ACEI/ARB ☐ Nitrates

☐ Diuretics ☐ Others

☐ Statin ☐ OHA ☐ Insulin

Antiplatelets

☐ Aspirin ☐ Clopidogrel

Examination

☐ Pallor ☐ Clubbing ☐ Cyanosis ☐ Bilateral Pedal Oedema

Pulse Rate | Systolic BP | Diastolic BP | ☐ JVP Elevated

Height | Weight | BMI | WC

Killip Class

☐ None

☐ Rales

☐ Acute Pulmonary Edema

☐ Cardiogenic Shock


Investigations
Hb
TC
Bl. Urea
S.Creatinine
RBS at Admission
T. Cholesterol
HDL
LDL
Triglycerides
FBS
CK-MB at 6 hrs
CK-MB at 24 hours
Trop T
Positive ASO titre
PT at 3 hrs
PT at 6 hrs
PT at 9 hrs
INR at 3 hrs
INR at 6 hrs
INR at 9 hrs
aPTT at 3hrs
aPTT at 6 hrs
aPTT at 9 hrs
ECG
NSTEMI
STEMI
WALL
Echo
RWMA
LV Dysfunction
Ejection fraction
Thrombolysis
Time of Index Pain
Time of Arrival at Hospital
Time Interval in Hours
Time of Thrombolysis
Time of Heparinisation
Thrombolysis successful
In Hospital Follow Up
Chest pain
Heart failure
Death
SVT
VT
VF
Ventricular ectopics
TIMI Score
Death by Day 15
Death by Day 30

CERTIFICATE OF CLEARANCE

K.A.P.VISWANATHAM GOVT. MEDICAL COLLEGE
TIRUCHIRAPALLI -1
INSTITUTIONAL ETHICS COMMITTEE

CERTIFICATE OF CLEARANCE

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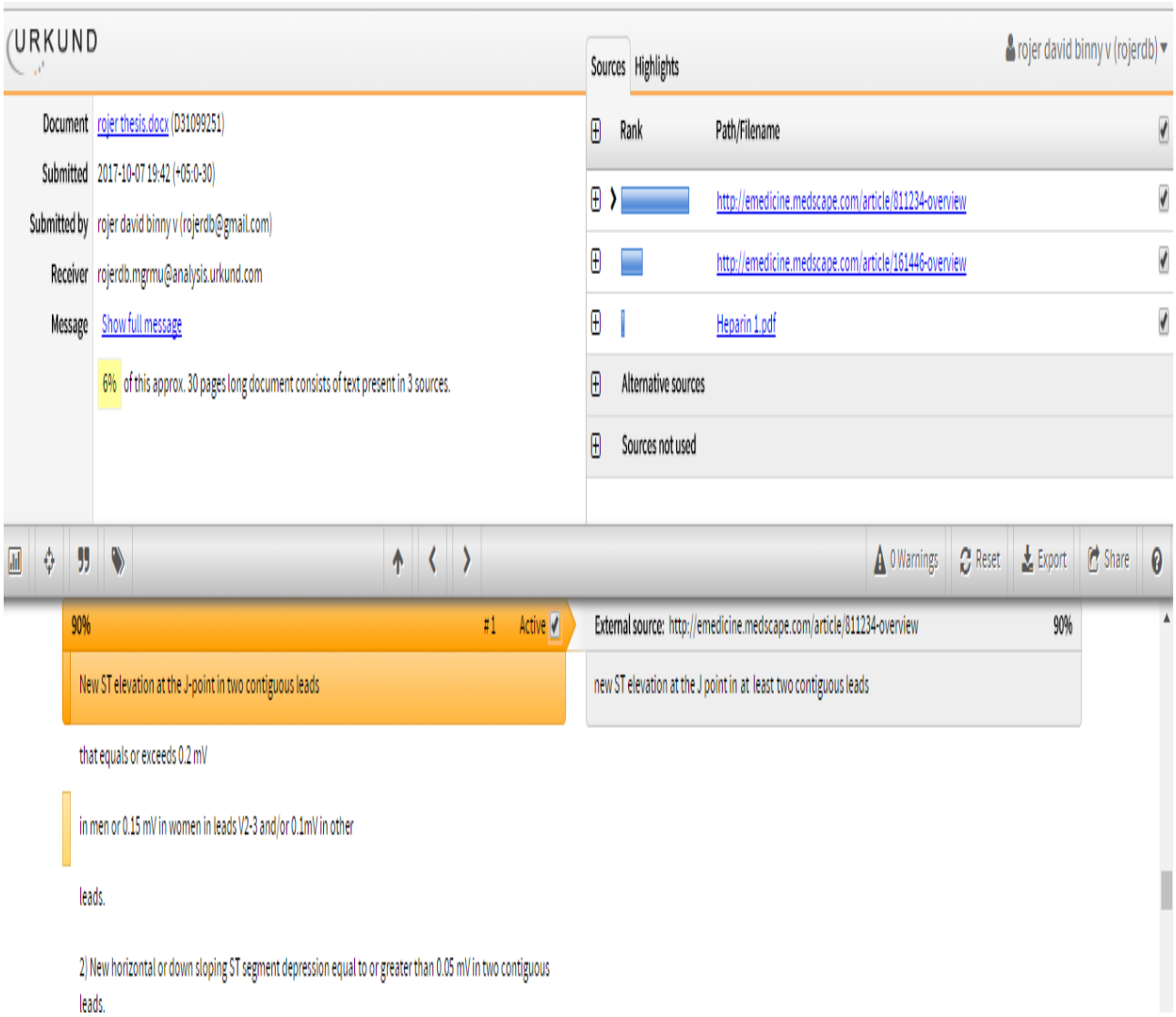
Dr.N.Jothi,MD.,
Prof. and HOD of Anaesthesia,
K.A.P.V.Govt.Medical College, Trichy
LAW PERSON
Mr.R.Rajendiran, ML.
Rtd. District Judge
Mrs.Kalavathy,
Ex.asura Social Worker, Trichy
Smt.S.Gayathri,
Lay person.

This is to certify that the project work titled A study of coagulation profile of patients thrombolysed with streptokinase in acute ST elevation myocardial infarction (STEMI) proposed by Dr.V.Rojer David Binny, part of fulfillment of M.D/M.S course in the subject of General Medicine for the year 2015-2018 by The Tamilnadu Dr.MGR Medical University has been cleared by the Ethics committee.

CHAIRMAN,
Institutional Ethics Committee
K.A.P.Viswanatham Govt. Medical College, Tiruchirapalli -1

PLAGIARISM REPORT



URKUND

Urkund Analysis Result

Analysed Document: rojer thesis.docx (D31099251)
Submitted: 10/7/2017 4:12:00 PM
Submitted By: rojerdb@gmail.com
Significance: 6 %

Sources included in the report:

Heparin 1.pdf (D21721389)
http://emedicine.medscape.com/article/811234-overview
http://emedicine.medscape.com/article/161446-overview

Instances where selected sources appear:

6

ABBREVIATIONS USED

MI	Myocardial infarction
UFH	Unfractionated heparin
STEMI	ST segment elevation myocardial infarction
NSTEMI	Non ST segment elevation myocardial infarction
ECG	Electro Cardiogram
PCI	Percutaneous coronary intervention
AWMI	Anterior wall myocardial infarction
IWMI	Inferior wall myocardial infarction
LWMI	Lateral wall myocardial infarction
HDL	High density lipoprotein
LDL	Low density lipoprotein
IHD	Ischemic heart disease
CVD	Cerebrovascular disease
CAD	Coronary artery disease
PT	Prothrombin Time
APTT	Activated partial thromboplastin time
DM	Diabetes mellitus
HTN	Hypertension
CABG	Coronary Artery Bypass Grafting
UA	Unstable Angina

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